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MINIREVIEWS

Angina bullosa hemorrhagica an enigmatic oral disease

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Abstract

Angina bullosa hemorrhagica (ABH) is an enigmatic oral disorder described for the first time by Badham in 1967 to define blisters with a hematic content in the oral cavity and oropharynx unrelated to any hematological, dermatological or systemic disease. The ABH is an uncommon disease of the oral cavity distinctively affecting adults, with the highest incidence over the 5th decade of life. This process is considered nowadays to have a multifactorial etiopathogenesis, where mild oral traumatisms can trigger the blisters in susceptible individuals. Certain association on the onset of the lesion with the chronic use of inhaled steroids and, more controversially, with triggering systemic disorders, such as, diabetes or hypertension has been described. Characteristically, the ABH blisters are acute and are located on the lining mucosa, more frequently on the soft palate. Usually, the lesions are solitary and rupture easily, resulting in a superficial ulceration that heals quickly without scarring. The histopathological analysis shows a subepithelial blister containing blood and direct immunofluorescence on the epithelium is negative. The differential diagnosis should consider all oral vesiculo-bullous disorders with hematic content, including mucocutaneos, hematological or cystic pathology. The diagnosis of ABH is clearly clinical, although the biopsy might be helpful on atypical or abnormally recurrent cases. The general prognosis of ABH is good and the treatment is symptomatic.

Key words: Angina; Bullosa; Hemorrhagica; Traumatic; Blister

Core tip: Although it is an uncommon disease, the angina bullosa hemorrhagica should be considered in the differential diagnosis of oral vesiculo-bullous processes. Acknowledging this entity will help in differentiating it from important mucocutaneous and hematological diseases such as pemphigus vulgaris, mucous membrane pemphigoid or coagulation disorders. In this review we analyze the main etiopathogenic, clinicopathological, diagnostic and therapeutic aspects of this enigmatic oral condition.

Alberdi-Navarro J, Gainza-Cirauqui ML, Prieto-Elías M, Aguirre-Urizar JM. Angina bullosa hemorrhagica an enigmatic oral disease. *World J Stomatol* 2015; 4(1): 1-7 Available from: URL: http://www.wjgnet.com/2218-6263/full/v4/i1/1.htm DOI: http://dx.doi.org/10.5321/wjs.v4.i1.1

CONCEPT

Angina bullosa haemorrhagica (ABH) is an uncommon and benign subepithelial disorder appearing as hematic blisters on the oral and oropharyngeal mucosa and no relation with any dermatological, haemostatic or systemic condition[1]. Badham[1] in 1967 defined these lesions with this term, although according to Stephenson *et al*[2] in 1987 and Grinspan *et al*[3] in 1999, similar lesions had been previously described by other authors such as Haryng[4] in 1890 referred to this condition as "Traumatic Oral Hemophlyctenosis" or Baliña[5] in 1933 as "Angina Ulcerosa Benigna" 1933. This entity has received multiple names, such as Benign Hemorrhagic Bullous Stomatitis[6] or Localized Oral Purpura[7]. In 1994 Kirtschig and Happle[8] named it "Stomatopompholyx hemorrhagica", as "angina" was an inadequate term for this disease. However, despite all the attempts in changing its name, ABH continues as the most commonly used term in the literature.

EPIDEMIOLOGICAL AND ETIOPATHOGENIC ASPECTS

The ABH is an uncommon oral pathology, although its real prevalence is unknown. The study performed by Mehrotra *et al*[9] in 2010 is the most accurate as they analyze the prevalence of oral pathologies of the soft tissue in a sample of 3030 Indian adults reporting a prevalence of ABH of only 0.03%. Retrospective studies show a prevalence of 0.5% on patients diagnosed with ABH in Oral Medicine and Oral Pathology clinics[3,10]. However, many authors[1,10-13] estimate a higher prevalence of this disease, justifying its rare diagnosis to its frequent asymptomatic character and the fast resolution of the lesions, which would lead the patient to seek less attention, thus to be undiagnosed.

This disease distinctively affects adult patients from the 3rd decade of life, with a peak incidence over the 5th decade[2,3,10,14-17].

Regarding the gender distribution, in his first description, Badham[1] observed a higher prevalence of ABH in women, although later published series of cases[2,3,10] have shown that the differences between genders are non-significant and, some authors[17], even describe a higher prevalence in males.

The etiopathogenesis of this lesion is yet unknown thus being considered nowadays as a multifactorial disease with local trauma on the oral mucosa as the trigger on susceptible individuals[16]. Several authors[1,3], have considered ABH an acquired disease without a recognized genetic component; however, some[2,18] have described certain familial predisposition in developing ABH.

Classically, it has been suggested that a loss of cohesion between the epithelium and the chorion can cause the rupture of the subepithelial capillaries after trauma and condition the emergence of a blood-containing blister[15].

Local trauma factors

An important percentage of the cases (35%-100%) report a known triggering traumatic event, with the intake of hard or crunchy foods as the most cited[2,10,13,15-17,19]. Nevertheless, it is worth mentioning that, in a study[3], only 24% of the patients could identify the traumatic factor. We believe that this datum is lower due to the retrospective character of many ABH studies that force the patient to remember the existence of a previous traumatic event[2].

Different foods are associated with ABH, including toasts, chips and hot meals[1]. Together with hard and crunchy foods (75%), a previous intake of acidic and citrus fruits has also been reported[17,18]. As an anecdote, other hard foods, such as a fish bone or a chicken bone, have been linked[19]. Along with food, beverage consumption has been associated with the onset of ABH, although the type and its characteristics are yet to be described[16].

Several clinical cases are associated to trauma from dental procedures, including impressions[2], dental preparations[20], a crown as a traumatic factor[21], certain conservative treatments[15], the injection of local anesthesia[22-24] or a periodontal treatment[25]. Isolated cases of ABH from other traumatisms have been described, including intubations or endoscopies[1,26], or even after coughing or sneezing roughly[11,15].

In 1987, Stephenson *et al*[2] suggested the suction habit as the main cause for the formation of these lesions; although, incidentally, none of the 30 patients from their study described this circumstance. Subsequently, de las Heras *et al*[27] described that the suction habit could lead to multiple ABH lesions.

Drugs

Together with local traumatic factors, certain inhaled drugs, mainly the chronic use of topical corticosteroids, have been associated with the onset of ABH[28,29]. High and Main[28] performed a study in 1988 in two groups of patients with asthma undergoing treatment with aerosols, one with and one without steroids. When comparing the incidence of ABH, lesions were present only in the group using steroids (35.7%). In these cases, the prolonged contact of the steroid with the oral mucosa may cause epithelial atrophy and may alter the distribution of the chorionic elastic fibers, which would weaken the epithelium-connective tissue junction, and would favor the onset of a subepithelial blister in a local traumatic event[19,28,29].

Another inhaled drug linked to the onset of ABH is

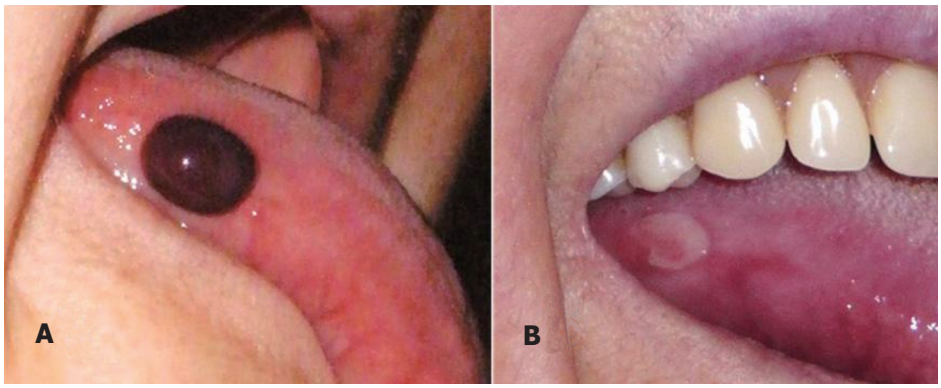

Figure 1 Clinical presentation of the disease. A: Blister on the right lateral border of the tongue; B: Superficial ulcer after rupture of the hemorrhagic bulla (4 d of evolution).

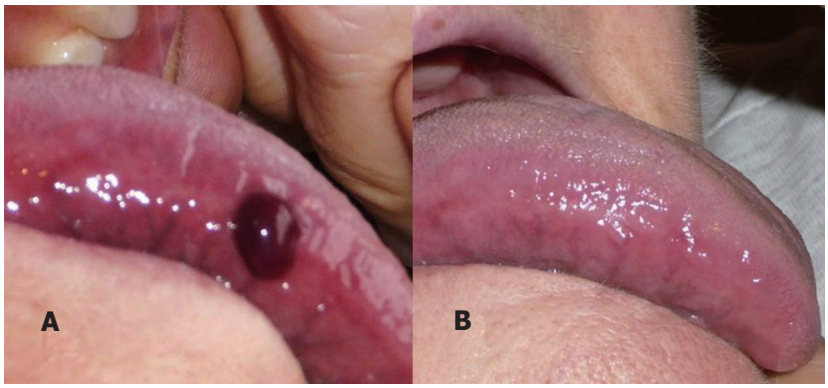

Figure 2 Presentation and resolution of a clinical case. Blister with blood content (angina bullosa hemorrhagica) on the border of the tonge (A) and full clinical resolution after 14 d of evolution (B).

Table 1 Association between angina bullosa hemorrhagica and diabetes mellitus and hypertension

Ref.	*n*	Diabetes	Hypertension
Grinspan *et al*[3]	54	24 (44%)[1]	0 (0%)
Giuliani *et al*[16]	8	1 (12.5%)	0 (0%)
Yamamoto *et al*[13]	11	4 (36.4%)	3 (27.3%)
Horie *et al*[17]	16	1 (6.25%)	6 (37.5%)
Deblauwe and van der Waal[11]	9	1 (11.1%)	0 (0%)
Serra *et al*[31]	4	0 (0%)	2 (50%)
Martini *et al*[19]	4	0 (0%)	2 (50%)
Rosa *et al*[10]	47	4 (8.5%)	17 (32.2%)

[1]Includes patients with altered serological values of glucose and family history of diabetes.

Ipratropium Bromide, an antimuscarinic bronchodilator[30].

Systemic diseases

Badham[1] described in his study certain association between ABH and systemic conditions, including menstruation in some of his patients.

Subsequently, ABH has been linked to different systemic processes, although this is still unfounded as its etiopathogenic base is yet to be described. The main systemic conditions associated with ABH are diabetes mellitus and hypertension (Table 1).

The high prevalence of diabetes, described only by Grinspan *et al*[3] in 1999 is worth mentioning as 44% of the ABH patients showed altered serological levels of glucose or family history of diabetes mellitus. It is possible that considering that both entities share the same age range and that diabetes has a high incidence among adults, it could be a coincidental relation and not a direct pathological association.

Regarding hypertension, several authors[10,17] outline circumstances similar to diabetes mellitus. Moreover, several cases of patients with chronic kidney failure are described in the literature[13,32,33].

CLINICAL CHARACTERISTICS

The characteristic lesion of ABH is a dark red-violet blister with a hematic content[1] (Figure 1A and Figure 2A).

Two types of patients have been distinguished according to its clinical presentation[15]. Some, the most frequent, have a large solitary lesion located in the soft palate and recurring spaced in time; others, less frequent, have a greater number of lesions in different locations and with a higher recurrence rate. Subsequent studies avoid separating into these subtypes as they distinguish the solitary lesion as the most frequent clinical presentation[2,3,10,18,16]. Nonetheless, in 30% of the patients multiple lesions are present, with up to 4

simultaneous lesions being described[15,34].

The formation of the blisters is characteristically acute as the lesions may appear abruptly within seconds[1,3,15,35]. The lesions have a diameter of 0.3 to 4 cm, but generally over 1 cm[2,3,15,17,25,33]. Despite most authors, Rosa *et al*[10], in their study on 47 patients, observed that most lesions measured less than 1 cm in diameter.

The lesions might cause mild unspecific discomfort for which it may be diagnosed casually on a dental revision[3,13,16,19,35]. However, Rosa *et al*[10], described pain, mainly of a mild intensity, in 36.1% of their patients.

In some cases, and previous to the blister formation, a burning or itching sensation, or even a stabbing pain has been described[15,36].

Regarding the location of the lesions, there is agreement in suggesting that the most affected site is the soft palate, followed by the borders of the tongue and the buccal mucosa[2,3,10,13-15,17,19]. Nonetheless, in addition to the above mentioned locations, cases have been described in the ventral surface of the tongue[2], the lip[15] and the floor of the mouth[3,15,16]. It is important to point out that all of these locations are part of the "lining mucosa" of the oral cavity which is non-keratinized. Some authors[2,15,27] have defended that the keratinized masticatory mucosa (hard palate, gingiva and lingual dorsum) remains unaffected in this pathology. Even so, several cases are described in these locations[25,32,33]. In addition to the intraoral involvement, Badham included lesions in the pharynx and esophagus[1].

The time the blister stays complete in the oral cavity is variable, from a few minutes to hours[2,8,14-16,35] or even days[32,34], and depends on the location and the size. When ruptured, generally spontaneously or while eating, its hematic content is emptied giving rise to an ulcerated area with minor symptomatology[2,3,16,19]. Martini *et al*[19], described the formation of petechiae in the periphery of the blister immediately after its rupture, which they suggest to be caused by a venous obstruction in the area, although it is unclear if it is a cause or a consequence of the blister. A similar event, although surrounding intact blisters, was described by Hopkins and Walter in 1985[15], defining it as an "ecchymotic halo". Furthermore, Grinspan *et al*[3], described that the blood in the blister may occasionally be coagulated.

Although the blister is the defining lesion of ABH, it is frail and the patient might seek attention for an unspecific ulcer instead (Figure 1B)[10,16,19]. These ulcers heal within 7-14 d without leaving scars (Figure 2B)[2,3,16].

The recurrence of ABH lesions is frequent, between 25% and 100% of the cases[2,3,10,15,16,19,31], with the lesions appearing in the same location or on another area of the oral mucosa[3]. It is interesting that, despite most authors, Horie *et al*[17] show no recurrence in a series of 16 cases.

The frequency of recurrence of ABH is variable, with patients reporting lesions only once or twice per year while others show them continuously[2,3,15,16]. Recurrences for more than 24 years have been described[2,33].

HISTOPATHOLOGICAL CHARACTERISTICS

The cases where the ABH lesions have been biopsied before its rupture show a subepithelial blister with a hematic content and an atrophic squamous epithelium surrounding the lesion[2]. A mild perilesional inflammatory infiltrate, generally chronic, is also observed[2,3]. In certain cases, an abundant acute subepithelial inflammatory infiltrate with a certain perivascular disposition has been described[34]. The biopsy of the ulcer formed after the rupture of the blister shows an unspecific ulcer with chronic inflammatory infiltrate, mainly lymphocytic[16].

Silver special staining has shown a decrease in elastic fibers in the chorion[29]. In addition, a capillary vascular hypertrophy, similar to that of patients with diabetes or porphyria, has been described[3].

Studies with direct immunofluorescence may be useful to rule out other oral vesiculo-bullous diseases of an immunological basis and with a poorer prognosis, such as Pempighus Vulgaris or Mucous Membrane Pemphigoid[14]. Unlike these diseases, direct immunofluorescence of ABH lesions is negative for IgA, IgG, IgM, fibrinogen and the C3 complement fraction. However, Stephenson *et al*[2] described certain basal positivity for IgG and C3 in some cases.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of ABH should be made with all vesiculo-bullous diseases of the oral cavity, including hematological disorders, mucocutaneous immunological pathology and cystic pathology.

Some hematological pathologies, such as thrombocytopenia or the von Willebrand Disease, may present lesions similar to ABH[14,37] Therefore, a complete blood test should always be performed, including coagulation tests which in these cases are altered, while in ABH are normal[3,14,16].

In addition to these pathologies, Serra *et al*[31] mention other hematological entities, including leukemia and vasculitis that should be considered in the differential diagnosis. In these cases, the lesions are usually multiple and widespread appearing in other locations of the body and generally producing systemic symptoms.

The mucocutaneous immunological diseases are the most important differential diagnosis of ABH and should include pemphigus vulgaris, mucous membrane pemphigoid, lineal IgA disease, epidermolysis bullosa acquisita and bullous amyloidosis[16]. All of these pathologies have a characteristic immunological basis and sometimes have clinical or even histological

Table 2 Clinical differential diagnosis of angina bullosa hemorrhagica with mucocutaneous diseases of an immunological basis

Disease	Type of lesion	Content of the blister	Location	Cutaneous involvement	Involvement of other mucosal membranes
Angina bullosa hemorrhagica	Subepithelial blister	Hematic	LM (soft palate)	No	Oropharynx and esophageal
Mucous membrane pemphigoid[38]	Subepithelial blisters and vesicles	Serous and serohematic	MM and LM (gingiva)	Yes	Ocular, genital, oropharynx, nasal and esophageal
Pemphigus vulgaris[39]	Intraepithelial blisters and vesicles	Serous	MM and LM (areas of friction)	Yes	Nasal, ocular, esophageal, genital, pharyngeal
Linear IgA disease[40]	Subepithelial blisters and vesicles	Serous and serohematic	MM and LM	Yes	Ocular, nasal, genital
Epidermolysis bullosa acquisita[41]	Subepithelial blister	Serous, serohematic or hematic	MM and LM	Yes	Ocular, anal, vaginal, esophageal (depending on the subtype)
Bullous amyloidosis[42]	Subepithelial blister	Hematic	MM and LM	Yes	Not described

LM: Lining mucosa; MM: Masticatory mucosa.

characteristics similar to ABH. The main clinical characteristics that differentiate these entities are shown in Table 2.

To perform a correct differential diagnosis on these entities, a good medical history is essential, focusing on the presence of lesions in skin or other mucosal membranes[14]. The most important differential diagnosis for patients with an ABH ulcer is, without a doubt, pemphigus vulgaris.

In cases of solitary lesions showing the typical characteristics of ABH (acute onset and associated to a traumatic event) a biopsy is often unnecessary[17]. The histopathological analysis should be performed only in cases with multiple or recurrent lesions or on atypical lesions. In these cases, together with the conventional hematoxylin and eosin histopathological analysis, it is convenient to perform direct immunofluorescence for IgA, IgG, IgM and C3 in order to exclude other mucocutaneous processes[2,14,16].

The differential diagnosis with oral cystic pathologies includes superficial mucocele. This lesion often shows acute clinical features generating a subepithelial blister that initially contains mucus but, after traumatic events, may contain blood and be mistaken with ABH[43].

Finally, some genetic syndromes with blisters containing blood in the oral cavity and oropharynx, such as the Kindler syndrome[44] or the vascular type of the Ehler-Danlos syndrome, should be excluded[45]. It is important to consider that the lesions of ABH are only present in adults, while on these processes, they appear in young people.

TREATMENT

Given the clinical characteristics of this disease, a specific treatment is unnecessary in most cases, recommending a symptomatic treatment of the lesions[2,3,15-17].

A complete blood test is necessary to rule out a possible systemic compromise while a histopathological analysis would be helpful in those cases with a complicated differential diagnosis.

The benign nature of the process should always be explained to the patients[2]. Given the possible traumatic etiology, this should be avoided by establishing general measures and eliminating all possible irritants[3,17]. Serra *et al*[31] recommend patients undergoing treatment with inhaled topical steroids to rinse with water after each use as a prevention measure of ABH.

In ABH patients with discomfort or pain, the treatment of the symptoms includes different drugs such as a mouthwash of benzydamine hydrochloride[2], several anti-inflammatory drugs[28], or even topical beclomethasone[32].

To avoid the superinfection of the ulcer resulting from the rupture of the blister, Hopkins and Walker[15] recommended rinsing with chlortetracycline. However, most authors[14,16,28], support the use of chlorhexidine gluconate mouthwashes in concentrations between 0.12%-0.25%.

To avoid possible recurrences, ascorbic acid and citroflavonoids have been suggested to be administered to the patients[3], without effective results reported.

The general prognosis for ABH is good; however, large lesions and on the soft palate and oropharynx may cause a feeling of suffocation due to a compromise of the upper airway, which leads the patient to seek urgent attention and even compromises his or her life[2,15,26,32,46]. Therefore, large blisters are recommended to be ruptured,

mainly those located in the soft palate and oropharynx, as to decrease the possibility of causing obstruction of the upper airway and avoiding an unpleasant choking sensation on the patient[2,15-17,36].

CONCLUSION

The ABH is an uncommon disease of the oral cavity and oropharynx that should be considered when a blister with a hematic content is observed. It is important for the dentist to acknowledge this condition as to differentiate it from other oral vesicular processes with a poorer prognosis such as Pemphigus Vulgaris, Mucous Membrane Pemphigoid or certain hematological diseases.

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Melkersson-Rosenthal syndrome

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Abstract

Melkersson-Rosenthal syndrome (MRS) is a rare, non-caseating granulomatous disorder of unknown etiology and undefined diagnostic criteria. The classical triad of recurrent orofacial edema, relapsing facial paralysis, and fissured tongue, is not frequently seen in its complete form, and many patients remain misdiagnosed or undiagnosed for years. The purpose of this study is to review the findings in the literature describing the Melkersson-Rosenthal syndrome with aim to identify its clinical and histopathological characteristics and correlate them with definitive diagnostic criteria and effective treatment modalities. A systematic review and analysis of more than 100 publications met eligibility criteria performed by the authors. Orofacial edema of unknown etiology is the most typical clinical feature of the Melkersson-Rosenthal syndrome. Its coexistence with of facial nerve palsy or fissured tongue could be characterized as an oligosymptomatic MRS. Many investigators suggest cheilitis granulomatosa as a monosymptomatic form of MRS, while patients with facial palsy and fissured tongue, without orofacial edema, should not be considered having MRS. Histological evidence is not necessary. Corticosteroids are generally accepted as the mainstay treatment.

Key words: Melkersson-Rosenthal syndrome; Orofacial swelling; Cheilitis granulomatosa; Facial nerve palsy; Fissured tongue

Core tip: Orofacial edema of unknown etiology is the most typical clinical feature of the Melkersson-Rosenthal syndrome. Many investigators suggest cheilitis granulomatosa as a monosymptomatic form of melkersson-Rosenthal syndrome (MRS). The coexistence of orofacial edema with facial nerve palsy or fissured tongue could be characterized as an oligosymptomatic MRS. Patients with facial palsy and fissured tongue, without orofacial edema, should not be considered having MRS. Histological evidence is not necessary. Corticosteroids are generally accepted as the mainstay treatment.

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INTRODUCTION

Melkersson-Rosenthal syndrome is a rare pathological entity of unidentified pathogenesis and equivocal diagnostic criteria[1]. All three classical melkersson-Rosenthal syndrome (MRS) signs of orofacial edema, facial nerve palsy and fissured tongue[2], as described by Melkersson[3] and Rosenthal[4], are not frequently encountered and many patients remain misdiagnosed or undiagnosed for years due to indefinite syndrome sub-classification[2,5-8].

The annual incidence of MSR is ranging between 0.2 and 0.3 in 100000 per year among various published studies[2,6,7,9-11], but the rarity of the disease in conjunction with the difficulty in diagnosis makes these estimations quite precarious. Although MRS may affect all age groups[12], typically at least one of its symptoms appears before the fifth decade of life[10,13]. Many studies show a slight predilection for females[2,7,13], while equal female: male ratio[10] or male predominance[14] has also been reported.

The etiology of Melkersson–Rosenthal syndrome still remains unidentified. Although Crohn's disease, sarcoidosis, herpes viruses' infection, allergic reactions, and autoimmune diseases have been considered as possible causes of the syndrome[2,9,10,12,15-28], a definite pathogenetic association failed to be demonstrated by solid scientific evidence. Familial inheritance has also been assumed[5,8,15,29].

The purpose of this study is to review the associated with Melkersson-Rosenthal syndrome literature citations with aim to identify its clinical and histopathological characteristics and correlate them with definitive diagnostic criteria and effective treatment modalities.

STUDY STRATEGY

A systematic review and analysis of more than 100 publications met eligibility criteria performed by the authors. The search of literature references based on the MEDLINE with subject keywords included five main categories: Melkersson-Rosenthal syndrome, orofacial edema, cheilitis granulomatosa, facial paralysis and fissured tongue. Most of these studies have been conducted at departments of dermatology, oral and maxillofacial surgery, oral pathology and plastic surgery.

RESEARCH

Diagnosis

The most dominant manifestation of MRS is asymptomatic orofacial granulomatous edema[5,10,13,14,19,20,24,25,30]. Lip localization (cheilitis granulomatosa) is perhaps the most frequently encountered type of the MRS associated edema[10,12,14,30,31] while cheeks, tongue or eyelids involvement has also been reported[2,10,13,14,30]. The patients may experience recurrent short episodes of the edema for many years, which gradually becoming more persistent[3,8,10]. It may clinically mimic angioedema, but it last longer and it does not respond to antihistamines administration[32].

Unilateral or bilateral peripheral facial nerve palsy, indistinguishable from Bell's palsy, is another commonly encountered manifestation of MRS[7,13,17,30-33]. Facial nerve involvement could become permanent after recurrent episodes of shorten duration[13]. Palsies of other cranial nerves have also been reported[34].

The fissured tongue (lingua plicata), although found in one third to one half of MRS patients, could valuably assists in diagnosis[9,13,19,20,23-25,30,32,35]. Fissured tongue is defined the presence of at least 2 mm deep and 15 mm long grooves crossing the dorsum or margins of the tongue[36].

MRS patients may also experience recurring episodes of acute anterior uveitis[2,37]. Gastrointestinal symptoms[2], trigeminal neuralgia, psychotic episodes, migraine[9,12,23-28,30,31,38] or longstanding immunologic and autoimmune disturbances[35], may also be encountered.

The associated with the MRS histopathological findings include non-caseating granuloma, giant cells and/or lymphocyte infiltration, and fibrosis[2,5,10,12,26], but their present is not necessary for the final diagnosis[12,34,39]. However, biopsy proofs could crucially assist in diagnostic process and therefore repeated biopsies during an acute edema episode are generally recommended in case of strong clinical suspicion of MRS with negative or inconclusive histopathological report[5,12,13,32,39].

Imaging investigations and dermatology, immunology, gastroenterology, and ophthalmology consultations are also recommended during differential diagnosis, in order other pathologic entities to be excluded[5,20,21,23,40-42].

Sub-classification of MRS

The diagnosis of a complete MRS requires the simultaneous or not presence of orofacial swelling, facial nerve palsy and fissured tongue[2-4,12]. However the complete form of the syndrome is found in no more than 20% of overall MRS cases[5,9,10,12-14,17,20,30].

The majority of literature evidence demonstrates orofacial edema, as the most important diagnostic feature of MRS, affecting almost all patients[12,14,34]. Many investigators suggest cheilitis granulomatosa as a monosymptomatic form of MRS[10,12,17]. The coexistence of orofacial edema with facial nerve palsy or fissured tongue could be characterized as an oligosymptomatic MRS[5,9,20,23,25]. Other minor and more rare signs and symptoms could also be considered as additional diagnostic criteria of the oligosymptomatic form of the syndrome[2,30,34]. Patients with facial palsy and fissured tongue, without orofacial edema, should not be considered having MRS[12,43].

Management

Although there is no consensus in therapeutic approach, corticosteroids are generally accepted as the mainstay in MRS management[9,13,20,23,25,35]. Systemic or intralesional corticosteroid administration has been demonstrated

to keep orofacial edema under control, while pain relievers and/or antibiotics may be also be indicated in some cases[44,45]. In case of unacceptable aesthetic consequences, associated with the orofacial edema, facial reconstructive surgery could be taken under consideration[5,31,46].

Corticosteroids are also considered to be the treatment of choice for MRS associated facial nerve paralysis[9,13,23,25,27]. Massage and electrical stimulation have also been described but remain of uncertain efficacy[8,46]. Follow-up of the patients diagnosed to have MRS should be in a regularly base due to its chronic and gradually progressive nature.

CONCLUSION

Melkersson–Rosenthal syndrome is a recurrent and gradually progressive pathologic entity of indefinite classification. Even though the etiology still remains unknown and various treatment modalities are often unsatisfactory, it could be relieving to the patients and the involved physicians to have MRS diagnosed.

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Oral lichenplanus: Etiology, pathogenesis, diagnosis, and management

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Abstract

Oral Lichen planus (OLP) is a common chronic mucocutaneous disorder with an immune mediated pathogenesis. Its appearance may vary from presence of keratotic to erythematous areas. Etiology of OLP is unknown, but it is thought to be the result of an autoimmune process with an unknown predisposing factor. Oral lichen planus is a complex and poorly understood clinical condition with periods of remissions and exacerbations. Management of the OLP is diversified with few lesions requiring treatment for years and few others are mild, requiring no treatment.

Key words: Mucocutaneous disease; Lichen planus; Oral lichen planus; Autoimmunity; Corticosteroids

Core tip: Oral Lichen planus (OLP) is frequently encountered by the dermatologists and oral physician. Even though, lot of research is carried out on this disease, still the precise etiopathogenesis and treatment is controversial. As there is a risk of malignant potential reported with this disease, early diagnosis and proper management of the patient is necessary. The present article reviews the OLP briefly about its etiology, pathogenesis, diagnosis and various treatment aspects available.

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INTRODUCTION

Lichen planus is a mucocutaneous disorder which involves various mucosal surfaces either alone or along with involvement of skin. It most commonly involves the oral mucosa when compared with other mucosal sites[1]. Oral lichen planus (OLP) is a disease of unknown etiology affecting stratified squamous epithelia[2]. In isolated OLP, only oral lesions will exist[3]. The disease

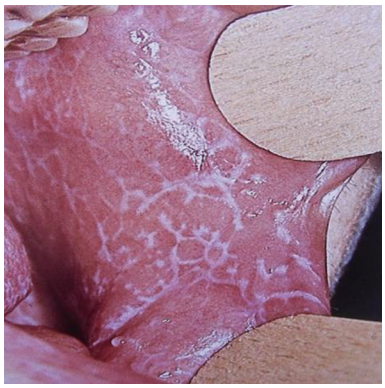

Figure 1 Reticular form of oral lichen planus.

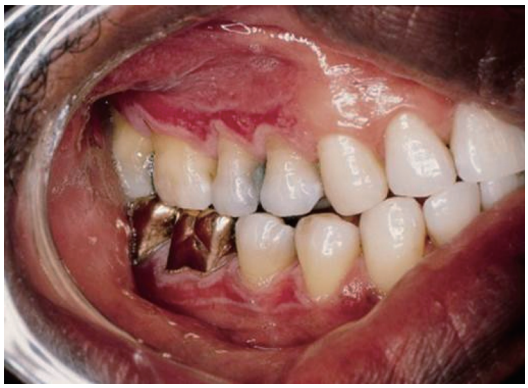

Figure 2 Atrophic form of oral lichen planus.

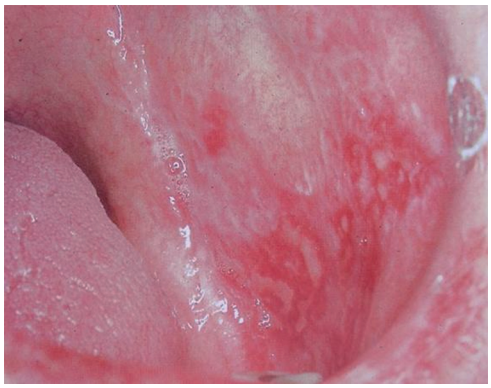

Figure 3 Erosive form of oral lichen planus.

affects 0.5%-2% of the general population. This disease most commonly involves middle aged patients of 30-60 years age group and females are more prone than males with a ratio of 1.4:1. OLP can be seen rarely in children and young adults[4,5]. OLP should be considered as a potentially malignant disorder because there is a relationship between oral cancer and OLP, although the degree of risk involved is variable[6].

The purpose of this review is to provide an update of the etiopathogenesis, clinical features, histological features, Diagnosis and management of OLP.

Clinical features of oral lichen planus

Oral Lichen planus was first described clinically by Erasmus Wilson in 1869 and histologically by Dubdreuilh in the year 1906[7]. Cutaneous lichen planus is recurrent, pruritic[8,9] and non-contagious[10]. Oral lichen planus rarely involves other sites like scalp, nails, esophagus, larynx and conjunctivae. OLP is gradual in onset and patients are unaware of the disease. Initially patients may present with roughening of oral mucosa, burning sensation and pain in oral mucosa to hot and spicy foods. Later red or white patches over the mucosa may appear which gradually progresses to oral ulcerations. The clinical history includes phases of remission and exacerbation[11].

The clinical presentation of oral Lichen planus resembles many other diseases. It can have many clinical presentations. In 1968, Andreasen divided OLP into 6 clinical forms: reticular, papular, plaque like, atrophic, erosive and bullous[12]. These forms may present either simultaneously or individually. Based on the predominant clinical morphology it will be labeled as specific form and the predominant morphology may change over time. Older individuals usually presents with more severe forms (erythematous/atrophic, erosive)[13].

The clinical forms described by Andreasen were made simple by other authors who classified lichen planus grossly into three types: Reticular, atropic or erythematous and erosive[14]. The reticular form (Figure 1) is the most common type. It clinically presents as papules and plaques with interlacing white keratotic lines (wickham's striae) surrounded by an erythematous border. Wickham's striae are usually bilateral and seen on buccal mucosa, mucobuccal fold, gingiva and rarely on palate, tongue and lips. This type is reportedly more common in males than females and it is usually asymptomatic[15]. OLP usually present as a bilateral symmetrical lesion or involves multiple areas individually[16]. OLP involving the gingiva is termed as "desquamative gingivitis" which clinically manifest as a fiery red erythema of attached gingiva. OLP lesions which are associated with patchy brown melanin deposits in the oral mucosa are termed as inflammatory melanosis[5].

Reticular form of oral lichen planus is usually asymptomatic. Atrophic/erythematous (Figure 2) and erosive/ulcerative (Figure 3) lesions are symptomatic. Symptoms include mucosal sensitivity, burning sensation and continuous debilitating pain. Oral lichen planus lesions usually persist for many years. OLP patients have periods of exacerbation and quiescence. Periods of exacerbation are generally associated with psychological stress and anxiety and during this time there is increased erythema or ulceration with increased pain and sensitivity[5]. OLP resulting from mechanical trauma either during dental treatments or due to cheek biting is termed as koebner phenomenon[13].

Malignant potential is high for atrophic and erosive forms of OLP[4,6], requiring regular follow up of patients. It should be done atleast 3 times in a year with more frequent examinations required for OLP with dysplasia. The symptoms of the disease such as burning sensation, loss of homogeneity in clinical appearance should be assessed thoroughly at each appointment and biopsy should be performed if required[17,18].

Etiology and pathogenesis

The exact etiology of this condition is unknown. Current literature suggests that T cell mediated immune mechanism is mainly implicated in the pathogenesis of OLP[5,13]. Pathogenesis of oral lichen planus may be antigen-specific and non-specific. Antigen-specific mechanisms include antigen presentation by basal keratinocytes and non-specific mechanisms include mast cell degranulation and matrix metalloproteinase (MMP) activation in OLP lesions. Both these mechanisms may combine which results in CD8+ cytotoxic T-cell accumulation in the superficial lamina propria followed by basement membrane disruption, intra-epithelial T-cell migration, and keratinocyte apoptosis. OLP chronicity may be due to deficient antigen-specific TGF-b1-mediated immunosuppression. This breakdown of normal oral mucosa could result in OLP[19].

Both endogenous and exogenous factors may cause cell-mediated immunity in a genetically susceptible patient and appears to play a major role in the pathogenesis of OLP[20]. The nature of the antigen implicated in OLP is uncertain, however numerous predisposing factors are known to induce OLP are identified. These are systemic medications, dental materials, chronic liver disease and hepatitis C virus, stress, genetics, tobacco chewing, Graft versus Host disease[16].

Systemic medications such as antimalarial drugs, non-steroidal anti-inflammatory drugs, antihypertensive agents, diuretics, oral hypoglycemic agents, beta blockers, pencilllins, sulfonamides, tetracyclines, heavy metals, thyroid preparations, antiretroviral medication have been reported to cause OLP[16,20-22].

The association of OLP with chronic liver disease was first suggested by Mokni *et al*[23] in 1991. Epidemiological evidences strongly suggest that Hepatitis C Virus may be an etiologic factor in OLP[24]. Association of OLP with several different autoimmune diseases such as alopecia areata, dermatitis herpetiformis, myasthenia gravis, *etc.* has been documented[20].

Periods of psychological stress and anxiety are associated with aggravation of OLP in most of the studies conducted so far[4,16,20,25,26]. Genetic predisposition also play a role in OLP pathogenesis[4,16]. Koebner phenomenon is a characteristic feature of cutaneous LP and is also observed in oral cavity. The erosive OLP lesions are most commonly seen in areas of trauma such as buccal mucosa and lateral surfaces of the tongue. These lesions may decrease in severity with the elimination of trauma[13,25]. Smoking, tobacco chewing, and betel nut chewing has been associated with the development of OLP in studies conducted in indian population[16,20]. Grinspan in 1963 found an interesting association between oral lichen planus, diabetes mellitus and hypertension, which he termed as Grinspan syndrome[27].

OLP is a T-cell mediated autoimmune disease in which the auto-cytotoxic CD8+ T cells trigger apoptosis of the basal cells of the oral epithelium. Initially keratinocyte antigen expression or unmasking of an antigen may occur followed by migration of T cells (mostly CD8+, and some CD4+ cells) into the epithelium. These migrated T cells are activated directly by antigen binding to major histocompatibility complex (MHC)-1 on keratinocyte or through activated CD4+ lymphocytes. In OLP, there will be up regulation of MHC-II expression along with increased number of Langerhan cells facilitating the antigen presentation to CD4+ cells, which activate CD8+ T cells through receptor interaction, interferon γ and IL-2. The activated CD8+ T cells trigger the apoptosis of basal keratinocytes by releasing tumor necrosis factor-α, granzyme B and by Fas–FasL mediated apoptosis. This results in loss of integrity of basement membrane. The MMP are principally involved in connective tissue matrix protein degradation[24].

DIAGNOSIS

The diagnosis can be made depending on the history, clinical and histopathological examination. However, in classical lesions, the diagnosis can be arrived based on clinical appearances (Wickham's striae, erythematous area) only. When skin lesions are also present, the accuracy of diagnosis is strengthened[21,28].

Differential diagnosis of reticular OLP includes leukoplakia, lichenoid reactions, lupus erythematosus and graft *vs* host disease. The differential diagnosis of erosive OLP includes chronic cheek chewing, hypersensitivity mucositis, chronic candidiasis, discoid lupus erythematosus, squamous cell carcinoma, benign mucous membrane pemphigoid, pemphigus vulgaris and erythema multiforme[21,28].

It is sometimes difficult to clinically diagnose "desquamative gingivitis" when lesions in other sites are absent. Mucous membrane pemphigoid, pemphigus vulgaris and OLP may present as desquamative gingivitis of very similar clinical aspect[29]. Biopsy is the gold standard for the diagnosis of OLP. The biopsy should include marginal tissue containing both lesional and normal-appearing areas. OLP can be distinguished from other chronic white or ulcerative oral lesions including reactive keratoses, chronic hyperplastic candidosis, epithelial dysplasia, discoid lupus erythematosus, gastrointestinal disease or anemic states with the help of histopathological examination[5,30].

Direct and indirect immunofluorescent studies, direct oral microscopy and enzyme linked immunosorbent assays can be helpful in reaching a diagnosis for

problematic cases and to exclude malignancy. Among these, the most important being the Immunofluorescent studies which are helpful in making a diagnosis in cases of OLP that may resemble other diseases[20,28,29,31,32].

Histopathological features

The histological features of OLP are similar to cutaneous lichen planus. These were first described by Dubreuill in 1906 and later by Shklar[16,33]. The histopathological features of OLP are characterized by a dense sub-epithelial lympho-histiocytic infiltrate, increased numbers of intra-epithelial lymphocytes and degeneration of basal keratinocytes. Degenerating basal keratinocytes form colloid bodies which appear as homogenous eosinophilic globules[5]. Colloid/civatte/cytoid/hyaline bodies are round and are seen either in the lower layers of the epithelium or within the upper layers of the connective tissue. These represent degenerated epithelial cells or phagocytosed epithelial cell remnants within macrophages[33]. The ultrastructure of colloid bodies revealed that these are apoptotic keratinocytes and the end-labeling method demonstrated DNA fragmentation in these cells. Epithelial basement membrane changes are also common in OLP and consist of breaks, branches, duplications and disruption of the basal keratinocyte anchoring elements (hemidesmosomes, filaments and fibrils). These changes like degeneration of basal keratinocytes, disruption of the epithelial basement membrane and basal keratinocyte anchoring elements together lead to produce weakness at the epithelial-connective tissue interface which results in histological cleft formation (Max-Joseph space) and blisters in oral mucosa. Parakeratosis, acanthosis and "saw-tooth" rete peg formation may be seen[5].

Absence of basal cell liquefaction, atypical cytomorphology, heterogeneous population of infiltrate, nucleus enlargement, blunted rete ridges, increased mitotic figures, absence of civatte bodies, abnormal keratinization will help to rule out the definitive diagnosis of OLP[34]. One study suggested that Colloid bodies can be helpful to differentiate oral lichen planus from oral lichenoid reaction. The location of colloid bodies is either in epithelium or connective tissue but usually close to the epithelium-connective tissue junction in case of OLP, while these were mostly seen in lower spinous layer of epithelium in case of oral lichenoid reaction[35]. Certain times, the histopathological features are equivocal or do not agree with clinical picture. Another biopsy may be necessary to confirm the diagnosis of OLP by immunofluorescence[21].

Direct Immunofluorescent examination of tissue in case of OLP demonstrates deposition of fibrinogen along the basement membrane zone[21] and colloid bodies stain for immunoglobulins IgA, IgG, and IgM[33]. Although the existence of fibrin deposition at the mucosal submucosal interface, within vessels and the presence of colloid bodies is highly sensitive for a diagnosis of LP, but it lacks specificity[31]. The sensitivity of direct immunofluorescence is positive for 65.8% of the patients with OLP[28]. Direct immunofluorescence is most sensitive when the tissue taken from buccal floor, upper labial mucosa, hard palate and mucosa of the cheek. It is less sensitive when the tissue taken from the gingiva and the dorsum of the tongue. Use of punch biopsy technique instead of conventional biopsy is better to detect the disease in direct immunofluorescence[28]. There is no difference in the sensitivity of direct immunofluorescence between biopsies performed in perilesional tissue (radius of up to 1 cm from the lesion) and distant tissue (radius greater than 1 cm). This occurs because the immune deposit may be present in the entire oral tissue, not only close to the lesion. Distant sites also provide more sample options when tissue extraction is difficult[28].

Direct oral microscopy technique is noninvasive which helps in clinical examination of oral cavity. This is based on the principle of colposcopy used by gynecologists and dermoscopy used by the dermatologists. This is used in a study conducted by Drogoszewska *et al*[32] for determing the site for biopsy and for clinical diagnosis of OLP. The principle behind usage of oral microscopy is to reveal precancerous lesion of oral mucosa in subclinical phase in order to begin the treatment as early as possible and to prevent malignant transformation. In their study they have done the direct oral microscopy by using a Leisegang colposcope, model BG/LED Y/C type 3ML. The results of their study showed that direct oral microscopy provides an alternative to clinical examination with the naked eye for choosing most appropriate biopsy site so that it is helpful in early detection of malignant changes of OLP and helps in early intervention of malignancy[32].

Management of OLP

As the immunopathogenesis of OLP is unclear, the clinical management of OLP poses considerable difficulty to the dermatologist and oral physician[36]. Currently there is no cure for oral lichen planus[2,13,21,37].

Reticular OLP is often asymptomatic and require no treatment[4,16,36], whereas atrophic, erosive forms can cause symptoms. Symptomatic OLP require therapy and treatment of OLP should be initiated after careful evaluation of patient's medical history, psychological state, treatment compliance and possible drug interactions while evaluating the cost effectiveness of any treatment modality[36]. When a medication is suspected that it is causing oral lichenoid lesions, then that drug should be discontinued[36,37]. OLP with involvement of the gingiva may be associated with deposition of plaque and calculus. Maintaining good oral hygiene by effective plaque control measures like supragingival scaling, oral hygiene instruction is essential which can enhance healing of the lesions and also decreases the painful symptoms of OLP[36,38]. Mechanical trauma of dental procedures, rough dental

restorations, friction from sharp cusps and poorly fitting dental prostheses can be exacerbating factors of symptomatic OLP and these factors should be corrected[16,36].

Transformation of OLP to squamous cell carcinoma is most commonly seen in cases of OLP involving the palatal arch, tongue, labial mucosa and gingiva. Therefore, it is essential to differentiate lesions of OLP as OLP with dysplasia and without dysplasia[34]. It has been suggested that regular follow-up of patients with OLP without dysplasia should be performed for at least every 4 mo. More frequent examinations should be considered for patients of OLP with dysplasia[34]. Before initiating treatment for OLP, it should be confirmed by biopsy. Oral candidiasis can be caused by different treatment modalities used for OLP, therefore it is important to take care of oral candidiasis before initiating treatment and also during treatment of OLP[21]. Current treatment modalities are palliative and have varied efficacy. The usage of specific medication depends on the potential benefit *vs* side effect and it differs from patient to patient based on patient condition and physicians choice[13]. No treatment modality has proved to be curative for OLP. Therefore different drugs are used in a single patient which suggests the insufficiency of any one agent to provide relief to the patient[2]. Various treatment regimens are available for the management of symptomatic oral LP.

Treatment of inflammatory/symptomatic OLP

Corticosteroids: Corticosteroids till today remain the first line of treatment for OLP. These drugs can be administered topically, intralesionally or systemically.

The most widely accepted treatment of OLP involves use of topical or systemic corticosteroids[2]. Topical corticosteroids remain the mainstay and first line of OLP treatment[13]. The combination of systemic and topical steroid therapy is often effective in certain severe cases of OLP. Localized OLP lesions are treated with topical steroids either in the form of ointment or paste which can be applied two to four times daily after meals. Topical preparations are also available as lozenges or as a mouthwash or through an inhaler with a special adapter. The dosage and specific preparations are based on the individual patient's needs. Steroid mouthrinse twice daily after food is effective method of treating generalized oral lesions[5,37,39]. Commonly used preparations include 0.025% or 0.05% clobetasol propionate gel, 0.1% or 0.05% betamethasone valerate gel, 0.05% fluocinonide gel, 0.05% clobetasol butyrate ointment or cream, 0.1% triamcinolone acetonide ointment[16,21,36,39-41], an aqueous suspension of triamcinolone acetonide 0.1% or 0.3% or 0.5% as oral rinse[37,42], dexamethasone elixir (5 mL of a 5 mg/5 mL suspension) as a mouth rinse[13] or 0.1% mouthwash[43], Hydrocortisone hemisuccinate in aqueous solution, betamethasone valerate pellets or aerosol or clobetasol propionate mouthwash[36,40].

Patients are adviced to apply a thin layer of the prescribed topical corticosteroid, 3 times a day. The gel or ointment can be applied either directly or indirectly by mixing with equal parts of Orabase, a gelatin–pectin–sodium carboxymethylcellulose-based oral adhesive paste which facilitates adhesion to the gingival tissues. The choice of delivery vehicle can be changed depending on clinician and patient preference. Oral application with a gel preparation is superior compared to other routes of administration. In patients with widespread symptomatic lesions, mouthwashes and aerosols are advised as direct mucosal application of topical medication will be uncomfortable to the patient. Patients should be instructed to gargle with 5 mL of the solution for 2 min after meals and at bedtime[21]. The topical steroid application is superior compared to systemic administration because of few side effects. Adverse effects include discomfort on application, thinning of the oral mucosa and candidiasis. Topical preparations of more potent corticosteroids can cause adrenal suppression. The signs and symptoms of OLP are usually improved within 8 wk of therapy with the use of topical steroid preparations[21,40]. Prolonged use of topical steroids mainly leads to development of oral candidiasis, so use of antifungal agents along with topical steroids is recommended. Fungal cultures also should be taken before, during and after the treatment[40,44].

Overall, topical steroids are used as a gel, cream, ointment with orabase, mouthwash, oral rinse, *etc*. The efficacy of the different topical steroid formulations are shown different results in various studies[36,40-44].

Persistent localized erosive OLP lesions are treated with Intralesional and perilesional injection of steroids with caution. Use of local anaesthetic with the preparation reduces the pain during injection. Candidiasis and atrophy of tissue are potential local complications. Intralesional injections of dexamethasone, hydrocortisone, triamcinolone acetonide, and methyl prednisolone are generally used[2,4,5,13,21,29,36,37,39].

Systemic corticosteroids should be reserved for diffuse erosive OLP, multisite disease and generalized atrophic or erosive OLP that do not respond to topical therapy. Depending on the severity of the disease, doses of prednisone 30-60 mg are given once daily for two to four weeks[36,39]. These drugs should be gradually tapered and potential adverse effects should be monitored during the treatment[13]. Clinical improvement of the OLP lesions is usually seen in majority of patients undergoing systemic prednisone therapy. Topical agent can be given in patients who are using prednisone once control is established[2].

Concurrently prescribing levamisole (150 mg/d) with prednisone will reduce the dose of prednisone. Use of Levamisole and prednisolone 25 mg/d for 3 consecutive days each week for 4-6 wk showed beneficial results in the management of erosive OLP[45,46].

Contraindications of steroid therapy include Hypers-

ensitivity, hypertension, viral infection, tuberculosis, diabetes mellitus and stomach ulcers[5].

In summary, most of the patients can be managed with corticosteroids. Use of Topical or intralesional or systemic steroid preparation is based on severity of the disease, systemic condition and adverse effects during the treatment. Intralesional agents are used in cases of ulcerations which do not respond to topical agents. Systemic agents are restricted for multisite disease, diffused disease and for OLP lesions which do not respond to topical agents.

Calcineurin inhibitors

Calcineurin is a protein phosphatase which activates transcription of Inter Leukin-2 there by stimulates the growth and differentiation of T-cell response. Cyclosporine, tacrolimus and pimecrolimus are calcineurin inhibitors are generally used in treatment of OLP[24].

Cyclosporine A is an immunosuppressive agent which is beneficial in cutaneous lichen planus[36]. Cyclosporine (100 mg/mL solution, 5 mL swish and spit three times daily) can be used as a mouth rinse in OLP patients who do not respond to topical corticosteroids[47-49]. Oral Cyclosporin A (5 to 6 mg/kg per day) is very effective in recalcitrant severe forms of the disease[48]. Recent studies compared the efficacy of cyclosporine solution and triamcinolone acetonide 0.1% in orabase in oral lichen planus lesions, these studies concluded that cyclosporine was not effective when compared with triamcinolone acetonide 0.1% in orabase[50,51]. Side-effects with cyclosporine include transient burning sensation, itching, swelling lips and petechial haemorrhages. These side effects, cost of the drug and also questionable efficacy of cyclosporine limits its use in OLP[49-51].

Tacrolimus is a potent immunosuppressive agent which can be used in topical form that can control symptoms of refractory erosive OLP. Studies showed that Tacrolimus ointment 0.1% is well tolerated and it is very effective in erosive OLP that did not respond to topical steroids. Most common adverse effect is local irritation due to burning sensation. Tacrolimus can be used as safe alternate to steroids when the lesions are resistant to the conventional treatment as there are less adverse effects with this drug. Topical tacrolimus helps to release the stress and improves the quality of life of patients suffering from OLP. Topical tacrolimus should be used for short period of about one month, as relapse of the lesions are seen within 6 to 12 mo of treatment cessation. Therefore prolonged or intermittent use of topical tacrolimus ointment in patients with symptomatic OLP may be recommended with constant monitoring. The United States Food and Drug Administration have recommended tacrolimus to be used for short periods of time because of a potential cancer risk from prolonged use. The efficacy of usage of tacrolimus remains to be clearly established in large, well-designed clinical studies[52-56].

Studies using 1% topical cream of pimecrolimus showed significant results in reducing ulceration and inflammation of lesion with better tolerance and relief from pain. Pimecrolimus has significant anti-inflammatory activity with low systemic immunosuppressive potential. Burning sensation is the common complaint experienced by the patients with the use of pimecrolimus[52,57,58]. Ibrahim *et al*[58] also observed the decresased expression of Fas in the immunohistochemical specimens after the treatment with pimecrolimus. Fas is an important molecule which is involved in apoptosis.

Retinoids

Various Topical retinoids such as 0.1% vitamin A, 0.05% tretinoin ointment, isotretinoin 0.1% gel, etretinate and fenretinide, with their immunomodulating properties are effective in OLP. Irritation, burning sensation are commonly observed with application of topical retinoids. Temporary reversal of white striae can be achieved with topical retinoids[13,24,36,42]. Systemic retinoids such as isotretinoin, temarotene, tretinoin have been used in cases of severe lichen planus with varied degree of success. The positive effects of retinoids should be weighed against their significant side effects[36].

Azathioprine

Azathioprine has potent immunosuppressive effects, can been used in the treatment of erosive OLP. There is a risk of malignancy with the long-term use of this drug. Azathioprine cannot be considered as better alternative to systemic steroids alone or systemic steroids in conjunction with topical steroids[36,39].

Lycopene

Lycopene is a fat-soluble carotenoid. It has antioxidant activity, also acts by inhibition of cancer cell proliferation and interference with growth factor stimulation. It has shown to be effective in the management of oral leukoplakia and in chemoprevention of oral cancer. Supplementing with 8 mg/d of lycopene for 8 wk showed favorable results of reduced burning sensation and decreased signs and symptoms of OLP in patients, in a placebo controlled study[59].

Aloe vera

Aloe vera (Aloe barbadensis Miller) is cactus like plant and it is a member of the Liliaceae family. There are few studies conducted using aloe vera gel or aloe vera in a aqueous suspension and it is also compared with the triamcinolone gel which showed beneficial effects in relieving symptoms of OLP. Further studies are required to prove the efficacy of aloe vera in the treatment of OLP[60-62].

Hyaluronic acid

Hyaluronic acid (HA) is a linear polymer of glucuronic

acid, N-acetylglucosamine disaccharide which helps in tissue healing. HA in the form of 0.2% gel showed transient improvement in decreasing the soreness associated with OLP in a placebo controlled double blind study[63].

Bacillus Calmette-Guerin polysaccharide nucleic acid

Bacillus Calmette-Guerin polysaccharide nucleic acid (BCG-PSN) is the third-generation BCG extract with various immunologic active materials including polysaccharide and nucleic acid. It has the ability to regulate the Th1/Th2 cytokine secretion in peripheral blood mononuclear cells (PBMC) of the OLP patients. In a study which compared the effectiveness of intralesional 0.5 mL BCG-PSN injection every alternative day with 10mg triamcinolone injection every week for about 2 wk showed equal effectiveness of both agents for erosive OLP. So BCG-PSN injections could be a promising therapeutic alternative for erosive OLP, especially for those insensitive or even resistant to glucocorticoids[64].

Anthocyanins

Anthocyanins are polyphenolic groups which block the spread of free radicals and are considered the main antioxidants of the plant kingdom. The extracts of grape seeds and grape skins contain anthocyanins. These are also present in other fruits, vegetables, chocolate, tea. Rivarola de Gutierrez *et al*[65] conducted a prospective, non-randomized study in 52 patients. Anthocyanins were administered in 100 mg/doses diluted in 5 mL of water, mouth rinses, during 5 min and spit, three times a day in 26 patients and control group received CP-NN cream (100 g of commercial preparation containing: 17-clobetasol propionate (micronized) 0.050 g, Neomycin (as sulfate) 0.350 g; Nystatin (micronized) 100.000 U/g. This was applied three times daily locally on lesions. There is improvement in the pain relief in patients with anthocyanins when compared with patients receiving CP-NN treatment[65].

Pharmacological agents like dapsone, doxycycline, griseofulvin, hydroxychloroquine sulphate, adalimumab, mycophenolates, efalizumab, cyclophosphamide, hydrochloroquine, phenytoin, mesalazine, interferon, glycyrrhizin, amitryptyline, amlexanox, curcuminoids, thalidomide, ignatia, purslane reported in the treatment of OLP. However, the main concerns with these are local and systemic side effects and lesion recurrence following withdrawal of treatment as fewer studies are reported with these agents. The cost-benefit and the safety profile of these drugs have to be more carefully considered and randomized controlled trials of these agents in larger groups of patients with OLP are recommended to clarify their effectiveness and safety profile[2,24,29,34,36,48,66,67].

NON-PHARMACOLOGICAL MODALITIES

Phototherapy or light therapy or heliotherapy has been widely used as an alternative therapy for the management of OLP. Different kinds of phototherapy include Ultra Violet (UV) phototherapy, photodynamic therapy and lasers[68].

UV Phototherapy

UVA treatment usually comprises UVA radiation (long wave length 315-400 nm Ultra Violet light) combined with a sensitizer (a chemical that increases the effect of UVA) called 8-methoxy psoralen. This form of treatment is referred to as PUVA (psoralen + UVA). To avoid PUVA side effects, photosensitization with topical 0.01% trioxsalen can be used for the treatment. Various side effects include nausea, eye symptoms, dizziness, paraesthesia and headache. PUVA therapy may be useful for severe forms of erosive OLP that do not respond to conventional treatment. Photochemotherapy with solar radiation has been introduced as an effective and cheaper alternative to PUVA. PUVA therapy has shown oncogenic potential, therefore it is not widely used and is discontinued for the treatment of OLP[4,16,36,68].

Photodynamic therapy

Photodynamic therapy (PDT) uses a photosensitizing compound (photosensitizer) which is activated at a specific wavelength of laser light which is known to destroy the targeted cell. PDT has shown positive results in management of head and neck tumors. The immunomodulatory activity of PDT also helpful in controlling the inflammation in OLP[2,16]. PDT with the use of different photosensitizers (methyl 5-aminolevulinate, phenothiazine dye methylene blue, Photolon®, a novel chlorin e6-derived photosensitizer) are used for the treatment of OLP and showed promising results in the treatment of OLP. The only PDT side effect reported was photosensitivity. However, further well-designed randomized controlled trials with larger numbers of patients with long follow-ups will be needed to evaluate the effectiveness of PDT in the treatment of OLP[68,69].

Lasers

Use of lasers for treatment of OLP is not recommended as the first choice of treatment, but it is suggested for use in patients who are unresponsive to topical corticosteroids[68]. Low-level laser therapy (LLLT; photobiostimulation, photobiomodulation) has physiological effects such as vasodilatation, enhancement of blood flow and lymph drainage, increased cellular metabolism, aggregation of prostaglandins, immunoglobulins and lymphokines, resulting in reduction of inflammation, immune response, and pain. Various low level lasers with different wavelenths, intensities, powers, durations, number of sessions, and therapeutic approaches (with or without tissue absorbent) have been used to treat oral lichen planus[70]. Few studies also reported the use of CO_2 laser, excimer laser for the treatment of OLP[68,71,72]. Use of LLLT, CO_2 lasers and excimer lasers are to be confirmed in well-designed

controlled trials with large number of patients[68].

Surgery

Surgical excision has been recommended for isolated plaques or non-healing erosions as it may cure the disease and also provides tissue for histopathologic examination. Surgical excision is not recommended in erosive and atrophic forms because of erosions in these forms and also due to recurrence of inflammation. Cryosurgery has been successful in cases of erosive OLP resistant to other treatment modalities. Recurrences are common with the use of cryosurgery[2,37,36].

Treatment of dysplastic OLP

The inflammatory component of OLP is treated with various above mentioned methods and additional approaches are required for assessing and treating dysplastic component in these cases[34].

CONCLUSION

Oral lichen planus is a chronic disease of oral mucosa. Patients of oral lichen planus have longer periods of disease activity with periods of remission and exacerbations and also there is a risk of malignant transformation over a long time. Therefore early diagnosis and treatment is mandatory with periodical follow up of the patients.

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Unraveling the role of epidermal growth factor receptor in oral lesions: Key to non surgical treatment modes

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Abstract

Epidermal growth factor receptor (EGFR) is a transmembrane receptor with tyrosine kinase activity, mediating actions of various growth factors including EGF, transforming growth factor-α, and neuregulins. Protein binding to ligand induces receptor modification, tyrosine autophosphorylation leading to cell signaling resulting in cellular proliferation. This receptor plays diverse roles in maintaining homeostasis and recent molecular advances identify that EGFR mutations are linked to several carcinomas. EGFR plays important roles in the development and maintenance of various oral structures, tooth development, eruption and morphogenesis. EGFR expression has also been studied in diverse oral pathologies like squamous cell carcinomas, potentially malignant lesions, lichen planus, salivary gland tumors and odontogenic cysts and tumours. The present review delves into the various general features of EGFR with an insight into its physiological and pathological role in the oral cavity. The clinical implications and upcoming role of EGFR inhibitors in the nonsurgical treatment of oral lesions has also been discussed.

Key words: Epidermal growth factor; Epidermal growth factor receptor; Oral pathology; Cetuximab

Core tip: This review addresses the importance and need to understand epidermal growth factor receptor (EGFR) related pathogenesis in oral lesions and the possible effectiveness of anti-EGFR agents in treating these conditions.

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INTRODUCTION

The epidermal growth factor receptor (EGFR) is nowadays being studied because of the possible role of

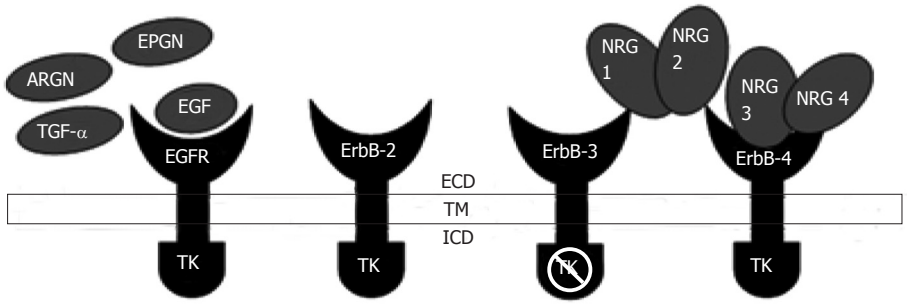

Figure 1 Epidermal growth factor receptor structure: Extracellular domain, transmembrane pass, intracellular domain, ligand binding, cysteine-rich domains. Intracellular domain includes the kinase domain and cytoplasmic tail. EGFR: Epidermal growth factor receptor; ECD: Extracellular domain; TM: Transmembrane pass; ICD: Intracellular domain; ARGN: Amphiregulin; EPGN: Epiregulin; TGF-α: Transforming growth factor alpha; TK: Tyrosine kinase; NRG: Neuregulin.

Figure 2 Epidermal growth factor receptor and its major ligands epidermal growth factor, transforming growth factor alpha, neuregulin, amphiregulin and epiregulin. ECD: Extracellular domain; TM: Transmembrane pass; ICD: Intracellular domain; LB: Ligand binding; CR: Cysteine-rich; KD: Kinase domain; CT: Cytoplasmic tail.

using EGFR inhibitors in the cancer chemotherapy[1]. EGFR is the prototypal member of four homologous transmembrane proteins and was the first protein in this family to have been sequenced and identified to have tyrosine kinase activity[2-5]. EGFR is also referred to as HER (human EGF receptor) and c-erbB1and is encoded by the *EGFR* gene located on chromosome 7p12. This transmembrane glycoprotein comprises of 1186 amino acids having three main parts; extracellular domain (ECD), transmembrane pass (TM) and intracellular domain (ICD)[2] (Figure 1).

In vertebrates, among the four EGFR family members (ErbB1, ErbB2, ErbB3 and ErbB4), overall similarity among the amino acids is about 50%[6]. The receptors EGFR family are together create an interacting system that receives and processes information that results in multiple cellular functions. EGFR binds to EGF, amphiregulin and TGF-α and ligands like betacellulin, heparin-binding EGF and epiregulin bind to the EGFR as well as ErbB4. The ErbB2/HER2/neu does not bind ligands and ErbB3/HER3 has an inactive kinase domain, and these receptors are thought to serve as co-receptors. Neuregulins 1 (NGR1) and Neuregulins 2 (NGR2) bind preferentially to ErbB3 and ErbB4 and the ligands NGR3 and NGR4 bind to ErbB4 (Figure 2). Ligand bonding initiates shape alteration that unmasks a "dimerization loop," thereby triggering receptor homo-dimerization or hetero-dimerization which causes tyrosine trans-phosphorylation leading to activation of downstream signaling cascades[7]. These pathways are often functionally interlinked and ideally should not be considered in isolation; however, for the sake of simplicity most authors discuss them individually[7-10].

The EGFR family is a diverse signaler and plays important physiological roles in determining cell lineage, organ morphogenesis, cell adaptation, motility, proliferation and apoptosis[5,7]. Damjanov *et al*[11] in 1986 conducted a study to identify EGFR in various tissues in human oral mucosa and suggested that membrane EGFR location depicts a more responsive cell than cytoplasmic EGFR localization This study said that it is likely that differential distribution of the EGFR to specific cell types and cellular compartments may signify adaptations that permit growth factor responsiveness in the surroundings of available ligand[11]. EGFR also interacts with RANK resulting in RANKL signaling pathways which helps in osteoclast differentiation and survival[12].

In general pathology EGFR plays a major role in human cancers. Aberrant EGFR signaling are initiated by several events, such as altered ligand production, receptor mutations or deletions and continuous signaling leading to uncontrolled cell multiplication, invasion, increased angiogenesis and metastasis[7,13-15]. EGFR also plays an important role in stopping autophagic cell death induced by death receptors which is one of the mechanisms that initiate cancer[14]. Another recent EGFR mechanism that was identified is the tyrosine kinase independent mode in which EGFR prevents cancer cells from apoptosis by regulating the basal intracellular glucose level *via* the sodium/glucose co transporter 1[15]. EGFR has varied effects in the prognosis of various cancers[13]. This is speculated to be an important reason for the aggressiveness and resistance to chemotherapy noticed in EGFR related epithelial tumors[16-19]. EGFR levels in normal cells usually ranges between 40000 and 100000 receptors per cell[19]. Enhanced EGFR expression are a notable characteristic of many epith-

elial carcinomas like glioblastoma, Non-small cell lung cancer, breast, colorectal, bladder, prostate and ovarian carcinomas[11,16-19].

EGFR IN ORAL PHYSIOLOGY

To understand EGFR related pathogenesis a proper understanding of its significance in physiology needed. EGFR plays important roles in the development and maintenance of various oral structures, tooth development, eruption and morphogenesis.

Hernández *et al*[20] in 1992 elicited the localization of epidermal growth factor and its receptor during tooth formation in rat embryos during embryonic days (E-16 to E-21) immunohistochemically. Another study by Heikinheimo *et al*[21] on role of EGFR in tooth development and few neoplastic odontogenic neoplasms concluded that that regulation of EGFR expression is developmentally determined in human odontogenesis. Furthermore, the odontogenic epithelium is the main target tissue for EGF, TGF-β and TGF-α and they may also be involved in odontogenic tumorigenesis[21]. Several authors like Wise *et al*[22], Shroff *et al*[23] and Cdhill *et al*[24] have proven that tooth follicle with the presence of EGFR and their ligands is essential for tooth eruption. EGFR and its ligands also mediates tooth morphogenesis as claimed by Hu *et al*[25].

On assessment of EGFR expression by Thesleff *et al*[26] it was seen that they intensely bind to the epithelial cell rests of Malassez concluding that they are responsive to the actions of EGF. Her study speculated that these epithelial rests may be activated whenever there is local rise of EGF ligand in that tissue milieu[26]. Another immunohistochemical analysis was performed in normal and pathological human gingival epithelia by Nordlund *et al*[27] which showed that basal layers of gingival proliferating cells in inflamed adult periodontitis cases, as well as the epithelial cell rests of Malassez bound to the antibody intensely signifying that EGF moderates epithelial growth and differentiation in periodontal tissues.

Also in recent research by O Häärä *et al*[28] it was evident that EGFR plays a role in formation of salivary gland by supporting the growth and development of the epithelium and survival of the mesenchyme.

EGFR IN ORAL PATHOLOGY

Various studies have analyzed EGFR expression in diverse oral lesions like squamous cell carcinomas[18,29-32], potentially malignant lesions[32-34], lichen planus[35,36] salivary gland tumors[37-39] and odontogenic cysts and tumours[40-44].

EGFR in head and neck squamous cell carcinoma

Head and neck squamous cell carcinoma (HNSCC) is increasing at an alarming rate with about 600000 patients being newly diagnosed annually. It was noted that most cases showing remission and metastasis are associated with poorer prognosis and a multitude of research is now being concentrated on understanding this disease and its relationship with EGFR pathways[18,19]. Heightened EGFR expression is observed in about 80%-90% HNSCC and often correlates with poorer prognosis, higher recurrence rate, advanced tumor stage and increased possibility of metastasis[13,18,19].

The HER 3 receptor was identified as most prognostic value in assessing tongue squamous cell carcinoma[31]. EGFR has been a recent target of anticancer therapies due to its critical roles in cellular homeostasis. *EGFR* mutations are found in four exons of the *EGFR* gene, exons 18 to 21. Exon 19 deletions and *exon 21* mutations account for most of these mutations. On genetic analysis it is seen that the *EGFR* mutation of deletion in exon 19 was implicated with squamous cell carcinoma development in few of the cases[45].

EGFR in potentially malignant lesions

EGFR over expression is an initial event in the squamous cell carcinoma of the head and neck carcinogenesis. On investigation done by Rautava *et al*[34] in dysplastic, developing and malignant oral epithelium it was seen that all the four family of EGFR receptors was seen in developing oral epithelium and to a lesser extent in mature oral epithelium[34]. An increase in EGFR immunoreactivity was seen in 61% and 54% of dysplasias and OSCC respectively. Its increased presence is also noted in "apparently normal" mucosa from cancer patients, when compared to healthy controls (field cancerization) and this over expression is observed to steadily increase analogous to observed histological abnormalities, from dysplasia to carcinoma *in situ*[34]. In normal mucosa EGFR positivity was seen only in the basal layers, whereas in leukoplakia the spinous and basal layers showed positivity and squamous cell carcinomas showed intense and increased positivity[46]. Another similarly designed study in dysplasias and SCC showed nearly all cells of the dysplastic epithelium showing positivity and in oral squamous cell carcinomas, the positivity in the tumor cells correlated inversely with cellular differentiation[47]. In other potentially malignant lesions like OSMF, it was found that there was a definite increase in EGFR expression along the differentiated layers of the oral epithelium[33]. In certain lesions like lichen planus, increased EGFR expression in the epithelial cells as well as the infiltrating lymphocytes are hypothesized to play a significant role in disease development[35,36].

EGFR expression in salivary gland lesions

EGFR expression has also been analyzed in various salivary gland lesions[37-39]. In a study done by Yamada *et al*[37] 1989 the immunohistochemical localization of EGFR was classified into two types, one the cell membrane-positive type found in epithelial tumor cells, and the other is the cytoplasm positivity seen in normal ductal

cells and luminal tumor cells of pleomorphic adenomas and mucoepidermoid carcinomas. In a recent study[38] done on pleomorphic adenomas (PA), mucoepidermoid carcinoma (MC) and adenoid cystic carcinoma (ACC), it was found that all of them expressed EGFR family receptors. ErbB-2 was seen to be commonly expressed and both membrane and cytoplasmic staining is noted. Enhanced scores of ErbB-2 membrane were more common in MEC as compared to ACC and PA suggestive of their role in pathogenesis of salivary gland neoplasms. Another study done in carcinoma ex Pleomorphic adenoma (CXPA), showed intense EGFR expression in the outer borders of CXPA, indicating that this receptor may be related to cell detachment and invasive potential of CXPA[39].

EGFR expression in odontogenic lesions

Numerous investigations have been done in odontogenic epithelium and related lesions in reference to EGFR expression[40-44]. Based on the various studies conducted in odontogenic cysts and tumors and it has been suggested that EGFR is related to the proliferative mechanisms in these lesions. Shrestha was one of the first to study the expression of EGFR in odontogenic lesions and he found increased expression of EGFR in these odontogenic cysts and tumors but no positivity in ameloblastomas[42]. Based on these findings the author then concluded that the proliferative pathways in ameloblastomas were diverse. However, most of the studies done later in ameloblastoma showed diverse results with most ameloblastomas giving EGFR positive immunoexpression[41,43]. EGFR expression was studied in the physiological odontogenic epithelium represented by the pericoronal follicle by da Silva Baumgart *et al*[42] and he hypothesized that understanding the staining patterns of EGFR in the follicles could provide vital clues to the origin of various odontogenic cysts and tumors. Other studies by Vered *et al*[43] and de Vicente *et al*[44] also give diverse findings.

METHODS OF EVALUATION OF EGFR

EGFR quantification can be done at the DNA, RNA or protein level[45]. *EGFR* mutations are known to occur in various carcinomas and they are studied by analyzing the chromosomes and DNA[46]. EGFR amplification which is noted in various lesions can be studied by gene amplifications assay which analyze at the DNA, RNA and the protein levels in tissue[47,48]. mRNA based methods of detection are prone to problems with RNA degradation and contamination.

EGFR protein levels quantified by western blot analysis and enzyme immunoassay, measure total receptor protein and provide no data on their location in the cell[49]. Immunohistochemistry is commonly used to evaluate EGFR protein levels and is arguably the most convenient method for analyzing clinical samples and give an idea about the cellular localization. However, the main disadvantage of immunohistochemistry is its lack of sensitivity and specificity in comparison to other methods. Further there is still no consensus of standard scoring criteria for the quantifying EGFR positivity in tissue specimens. Downstream markers and their analysis may also provide EGFR related information. The EGFR molecule has various downstream pathways of action and these molecules are of significance in studying specific lesions. Some of the most common downstream markers of significance are EGFR, p-EGFR, p-Akt, p-Erk, p-STAT3[50,51].

EGFR AND ITS CLINICAL IMPLICATIONS

The identification of chemo-therapeutic agents in the treatment of specific malignancies like leukemias and lymphomas have simplified and inspired new treatment perspectives of neoplasms. Since the advent and success of these treatment strategies, researchers all over the world are trying to open more avenues in the treatment of other malignancies. Ever since the discovery of EGF in 1960 and the isolation of EGFR by Cohen *et al*[52] in 1980 numerous studies are done to elucidate its role in cancer pathogenesis. Based on the work of many pioneers on EGFR agents John Mendelsohn conducted research focusing on EGFR and proposed EGFR as an anticancer target, especially in various carcinomas[17,53]. Control of EGFR signaling is likely to open new avenues of treatment in three main areas that include cell yield, organ restoration and management of cancer.

EGFR is the receptor most often found up regulated and its gene mutations are evident in a wide variety of human tumors like head and neck cancers, renal carcinomas, breast carcinomas, gliomas, colon cancers, non-small-cell lung carcinomas and pancreatic carcinomas[7,13,18,19,30,45,54,55]. Herbst *et al*[55] in 2002 stated that EGFR is one of the most important receptors critical for cell proliferation, differentiation and survival and related its dysregulation to be of significance in suppressing apoptosis, mediating neoplastic angiogenesis, increasing metastatic ability and resisting chemo and radiotherapy[55]. Several ongoing clinical trials on humans are presently testing anti-EGFR antibodies with many of them showing promising results for the future. The rationale behind EGFR therapies is that they compete with endogenous growth factors like EGF and transforming growth factor-alpha, for binding sites. Once bound EGFR blocks crucial downstream pathways thereby interfering with the growth of neoplasms expressing EGFR.

The rationale of using anti-EGFR agents in head and neck cancers is that EGFR is expressed in more than 90% of head and neck carcinomas and studies have shown that EGFR over expression is associated with decreased survival[1,18,29-32,49]. Also it is noted that increased EGFR expression occurs initially in carcinogenesis and is present even in premalignant oral lesions[32-34]. Finally

studies have also shown that inhibition of EGFR-TK pathway slows the growth of xenograft tumour models of head and neck. EGFR based chemotherapy can involve various methods[56]. This can be achieved by using directly acting anti-EGFR agents, by using tyrosine kinase inhibitors (TKIs) or agents that inhibit the downstream molecules in the EGFR pathway[56]. Amongst these, EGFR antibody Cetuximab and TKIs like Erlotinib and Gefitinib are being trialled in HNSCC. Understanding the molecular pathogenesis of the neoplasm will help in choosing the ideal therapeutic agent. For example EGFRvIII is caused by frame deletion mutations and is seen in 42% of HNSCC leading to growth of the tumor and provides resistance to antibody based treatment interventions.

In such situations, patients with EGFRvIII HNSCCs would possibly benefit better from tyrosine kinase inhibitors rather than EGFR antibody based treatment strategies[56,57].

Another important treatment possibility of the EGFR neoplasms is that anti-EGFR agents increase the radiosensitivity of several neoplasms. In a recent randomised phase III clinical trial attempted by Bonner *et al*[58] it was seen that simultaneous radiotherapy and chemotherapy with Cetuximab in head and neck cancer patients showed improved local tumour containment compared to radiotherapy alone[58]. The cause for increased radiation effects when combined with EGFR therapy are still obscure. Numerous other studies studying the efficacy of anti- EGFR agents are in the phase three trial[1,7,54,55,58]. Antisense oligonucleotides, ligand conjugates and immunoconjugates of EGFR are also used to inhibit EGFR activity. Other EGFR inhibitors like cetuximab-C225 are being extensively studied in head and neck carcinomas and are in the third phase of trial. However till date no drastic changes in treatment modalities have been experienced. Moreover, there are a lot of side effects associated with the use of EGFR which has rendered it use, unacceptable.

Vered in his article[43] mentions that adverse effects of anti-EGFR agents like C225 and ZD-1839 is usually observed in less than 15% of patients, and these effects may not occur with ameloblastoma, as these side effects could be avoided by intralesional administration of the anti-EGFR agents. Recently, a fully human anti-EGFR monoclonal antibody, vectibix-EGF was developed as a possible treatment for surgically compromised cases of ameloblastoma. However, clinical trials are yet to take place[43].

CONCLUSION

The EGF receptor is an important molecule in maintaining various pathways and homeostasis within an organism. It plays varied roles and its dysregulation is identified to be a key factor in various oral pathologies, especially HNSCC and ameloblastomas. Identifying ideal therapeutic target will enable the transition of treating these lesions using a non surgical modality thereby significantly reducing the mortality and morbidity of the patient. The receptor mediates it action through various pathways and the proper understanding of these will enable us to develop ideal treatment strategies to combat the various lesions. Several studies are now targeting these pathways, however, till now significant success has not been achieved in clinical trials using anti-EGFR agents in HNSCC. Several reasons suggested for this insensitivity are the multifactorial aetiology of head and neck carcinomas and lack of proper understanding of the various molecular pathways. More research needs to be focussed on the understanding of this molecule in future in order to bring the treatment of several debilitating neoplasms from the bench to the bedside.

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CASE REPORT

Unusual aggressive behavior of central giant cell granuloma following tooth extraction

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Abstract

Central giant cell granuloma (CGCG) is found exclusively in jaws. Its etiopathogenesis is unclear; however it is suggested that it can arise as a reactive response to trauma. This report describes an aggressive variety of CGCG which raises a question; can extraction of tooth modify the behavior of CGCG? A 46 years old male had reported with a rapidly increasing intraoral and extraoral swelling of lower jaw following tooth extraction. Radiographic examination revealed a large multilocular lesion involving the body and ramus of mandible which had been proved to be aggressive CGCG on histopathological examination. The importance of radiographic examination prior to extraction of teeth and importance of inclusion of CGCG in jaw swellings associated with mobility of teeth or failure of healing sockets is emphasized.

Key words: Aggressive; Central giant cell granuloma; Mandibular swelling; Extraction of teeth; Jaw

Core tip: This report describes an aggressive variety of central giant cell granuloma (CGCG) after extraction which raises a question; can extraction of tooth modify the behavior of CGCG? The importance of radiographic examination prior to extraction of teeth and importance of inclusion of CGCG in jaw swellings associated with mobility of teeth or failure of healing sockets is emphasized. Literature about clarity in clinical behavior, radiographic features and various treatment modalities of this one of the bony lesion of jaws are reviewed.

Dangore-Khasbage S, Degwekar SS, Bhowate RR, Hande AH, Lohe VK. Unusual aggressive behavior of central giant cell granuloma following tooth extraction. *World J Stomatol* 2015; 4(1): 29-34 Available from: URL: http://www.wjgnet.com/2218-6263/full/v4/i1/29.htm DOI: http://dx.doi.org/10.5321/wjs.v4.i1.29

INTRODUCTION

Central giant cell granuloma (CGCG) has unpredictable biologic behavior, non-specific radiographic features and is amenable to a plethora of treatment alternatives. A reactive response to trauma is the most accepted etiopathogenesis of CGCG[1-3]. This report describes a case of an aggressive variety of CGCG which was augmented following extraction of teeth. This is a rare presentation of CGCG and it suggests two important things, as delay in diagnosis has an important implication on morbidity and mortality of the patient. (1) The necessity of radiographic examination prior to extraction of teeth; and (2) importance of early histopathological examination, if extraction socket fails to heal should not be underestimated. Though abundant literature is available regarding this well known entity, case reports are still considered to be the source of information.

CASE REPORT

A 46 years old male reported to the Department of Oral Diagnosis and Medicine at Sharad Pawar Dental College and Hospital, Wardha, India, with a chief complaint of progressive extraoral and intraoral swelling on lower right back region of the jaw since 2 mo. History of present illness revealed that approximately three months ago patient had noticed mobility of the teeth in same region and all his molars were extracted from that quadrant. This had resulted in failure of healing of the extraction socket and development of rapidly enlarging extraoral and intraoral swelling 1 mo post-extraction. There was associated pain too. As a result of intraoral swelling the patient had difficulty in chewing, swallowing and speaking as these processes were aggravating the pain. There was no history of discharge from the swelling. The patient was of moderate build and healthy weight. The general systemic examination did not reveal any major illness.

On extraoral examination, there was diffuse swelling on lower right side of face resulting in marked facial asymmetry as shown in Figure 1. Palpation elicited that the swelling was bony hard, non-tender, fixed to the underlying structures and with no pulsations. Local Temperature was not raised. There were no signs of loss of sensory function.

Intraoral examination revealed missing lower right molars with an exophytic soft tissue growth from the residual socket and well-circumscribed ovoid swelling of approximately 4 cm × 6 cm in posterior region of right side of the mandible causing bucco-lingual expansion of the jaw with marks of indentation on overlying mucosa. (Figure 2). The swelling was firm in consistency, slightly tender and was fixed to underlying structures. On the basis of history and clinical features, provisional diagnosis was malignant tumor. Investigations were carried out to evaluate the case.

Lateral mandibular occlusal view showed single large multilocular radiolucent lesion having well defined periphery with predominant buccal and lingual expansion and thinned-out of cortical plates (Figure 3). A panoramic radiograph revealed a single large mutilocular radiolucent lesion involving the body (honey comb appearance) and ramus (soap bubble appearance) on right side of mandible extending anteroposteriorly from the canine to posterior border of ramus and superoinferiorly from sigmoid notch to inferior border of mandible in ramus region and from alveolar crest to inferior border of mandible in body

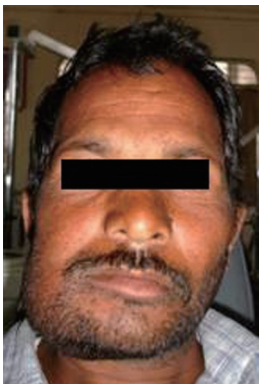

Figure 1 Diffuse swelling on lower right side of face.

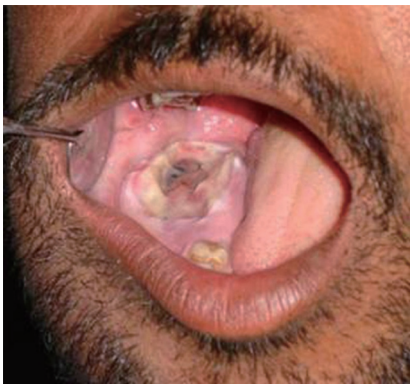

Figure 2 Swelling in molar region with marks of indentation on overlying mucosa.

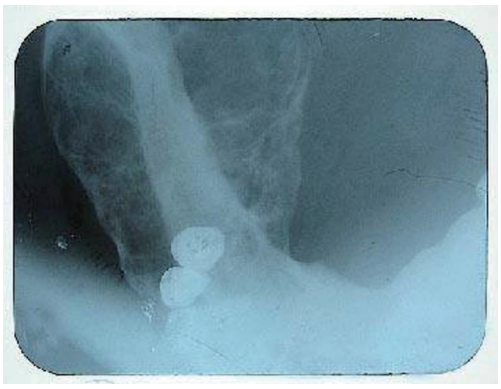

Figure 3 Mandibular lateral occlusal view showing predominantly buccal and lingual expansion with thinning of cortical plates.

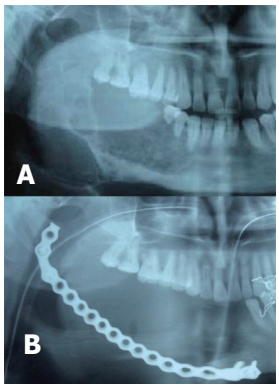

Figure 4 Cropped orthopantomograph showing (A) a multilocular lesion in body and ramus of mandible on right side (B) a surgical defect and radioopaque image of reconstruction plate.

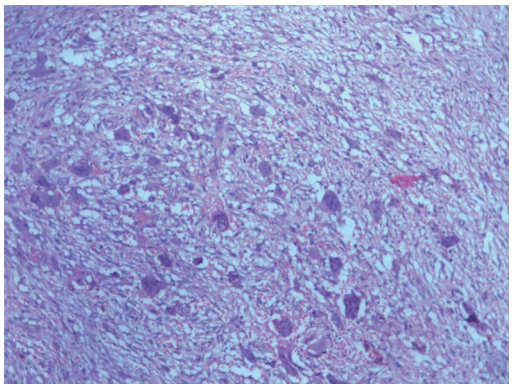

Figure 5 Photomicrograph showing multinucleated giant cells and spindle cells (10 ×).

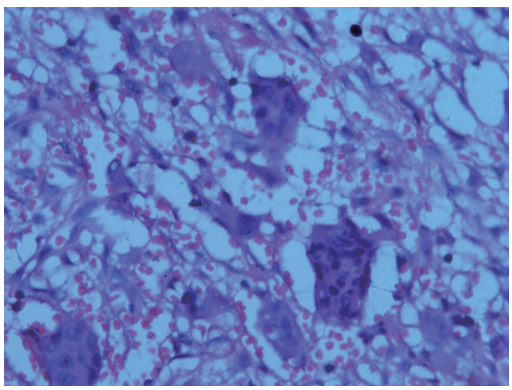

Figure 6 Photomicrograph showing multinucleated giant cells (40 ×).

region as illustrated in Figure 4A. The periphery of the lesion was well defined and scalloped. There was resorption and thinning of superior and inferior cortices, roots resorption as well as expansion at the inferior border of mandible.

On the basis of radiographic findings, probability of ameloblastoma was considered while various benign tumors and multilocular cysts were considered in differential diagnosis. The lesion was subjected to fine needle aspiration biopsy which was non productive. Then an incisional biopsy of the lesion was performed. Results of the biopsy showed the features suggestive of CGCG. An attempt was made to exclude the brown tumor of the hyperparathyroidism by undergoing biochemical tests (serum calcium, phosphorus, alkaline phosphates, and parathyroid hormone) which were within normal limits.

As surgery is the most accepted and traditional form of treatment for CGCG especially in the aggressive type and as there was absence of any systemic disease which could complicate the surgical treatment, surgery was chosen as a treatment of choice in this case.

Under general anesthesia the surgical excision of the lesion was performed by hemimandibulectomy and a reconstruction plate was inserted to repair the defect (Figure 4B). Post-operative healing was uneventful. The specimen was sent for histopathological examination. Hematoxylin and Eosin stained section showed highly cellular fibrous connective tissue stroma, which consisted of many plump fibroblasts, extravagated blood elements and numerous multinucleated giant cells, containing nuclei ranging from 5-20 in numbers and uniformly scattered throughout the lesion (Figures 5 and 6). The clinic-pathological diagnosis was compatible with aggressive CGCG. To confirm the origin of giant cells, the tissue was analyzed by immunohistochemistry by cytokeratin expression and giant cells were found to be positive for cytokeratin which confirmed the diagnosis (Figure 7). Clinical and radiographic examination after six months following surgery revealed uncomplicated recovery and no recurrence.

DISCUSSION

CGCG is an intra-osseous destructive lesion of jaws which has definite predilection for mandibular anterior region and has a tendency to cross the midline though controversial results also exist[4-7]. It rarely occurs in areas elsewhere other than the jaws like maxillary sinus, temporal bone, cranial vault and other bones of the craniofacial complex[4].

The etiopathogenesis of CGCG can be an exacerbated reparative process related to previous trauma and intraosseous hemorrhage that triggers the reactive granulomatous process[8,9]. In the present case, we can assume that trauma due to extraction might be responsible for change in behavior (rapid progress) of the lesion since the lesion grew rapidly and perforated intraorally after molar extractions. Similar such cases are rarely reported in the literature[9,10]. However, this type of clinical presentation is commonly observed in oral malignancy which was ruled out by radiographic examination in the present case.

Basically CGCG is a benign entity but based on its clinical behavior and radiographic features, it has been classified into non-aggressive and aggressive variety[1,11]. Aggressive CGCG is found in younger patients while in this regards, the present case was

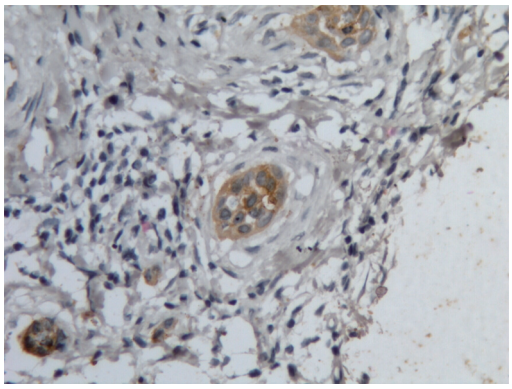

Figure 7 Immunohistochemical expresson of cytokeratin in giant cells.

distinct showing features of aggressive variety at advanced age.

Although aggressive lesion is expansive and invasive, paresthesia is usually not observed in these patients. However, Whitaker *et al*[5] reported paresthesia in 6% of their cases. Bataineh *et al*[12] have suggested the remedy to avoid distressing paresthesia or painful dysesthesia.

Amongst aggressive and non-aggressive types of CGCG, the controversial reports are observed in histologic differences. Few authors stated that there are no histologic differences between aggressive and non aggressive varieties[1,11]. Ahuja *et al*[13] reported high cellularity and a vesiculated fibroblastic population in aggressive CGCG while a minimal-moderate cellularity and a non vesiculated fibroblast population in non-aggressive cases[13]. Shetty *et al*[14] explained that the number of giant cells and number of nuclei within alone does not determine aggressive nature and recurrence of CGCG.

CGCG can present different radiological features, from small unilocular radiolucent lesions to extensive multilocular radiolucent areas. Wood *et al*[6] reported that the lesion may initially occur as a solitary-cyst like radiolucency and as it grows larger it may develop architecture of a soap bubble or honeycomb type of mutilocular radiolucency. Presence of wispy trabeculae within the lesion is the most significant radiographic sign associated with CGCG[2,5,6]. Though radiolucent is the commonest radiographic internal structure of CGCG (87.5%), Kaffe *et al*[7] have observed mixed (10%) and radiopaque (2.5) appearances too. Generally the periphery of CGCG is well defined but many times it presents with ill defined, diffused borders[7,15]. There may be a cortical radiopaque halo and dental displacement or root resorption[1,2]. Stavropoulos *et al*[16] and Jose *et al*[15] have found radicular resorption in 37% and 15.4% of cases respectively.

Overall above description suggests that the clinical and radiographic features of CGCG are non pathognomic and are often confused with several other lesions of the jaws that pose challenge to oral diagnostician. In this case also the provisional diagnosis considered was oral malignancy and radiological diagnosis was ameloblastoma. The present case justify radiographic examination before extraction of molars as failure of which resulted in an extensive lesion involving the body and ramus entirely due to modification in behavior of lesion following extractions. It also suggests inclusion of CGCG in jaw swellings associated with mobility of teeth and failure of healing sockets.

It is equally important to exclude brown tumors associated with hyperparathyroidism from CGCG as they share identical clinical and radiological features[15]. This differentiation depends on laboratory tests for investigating serum levels of calcium, phosphorus and alkaline phosphatase which, in cases of hyperparathyroidism, present alterations[2]. Ahuja *et al*[13] presented difficulty in diagnosing aggressive CGCG from Giant cell tumors with which they share similar histopathology, behavior and prognosis. Histologically, CGCG is indistinguishable from other giant cell lesions of the bone like cherubism and aneurysmal bone cyst too. But, in the present case immunohistochemcal expression of cytokeratin in giant cells helped to confirm the diagnosis. In multiregional cases of CGCG, cherubism, neurofibromatosis type 1 and Noonan syndrome must be considered in differential diagnosis[6,17]. A combination of CGCG with some other lesions like fibro osseous lesions called as hybrid lesions is also reported in the literature[18,19].

Traditionally the most accepted treatment of CGCG of the jaws is surgical while successful medicinal treatment modalities are also reported in the literature; each has got its own advantages and disadvantages[20-22]. Surgical approach may result in loss of teeth, disfigurement and loss of dental germs (in younger patients)[12,23]. Whitaker *et al*[5] have mentioned the recurrence rate of CGCG as 4% to 20% and the reasons were larger lesion and incomplete removal of the tumor. Radiation therapy is contraindicated in CGCG[3].

An alternative nonsurgical approaches are intralesional corticosteroid injections, calcitonin injections and subcutaneous interferon injections[20,23,24]. Weekly intralesional injections of corticosteroids are believed to inhibit the bone resorption by controlling proliferation and differentiation of osteoclasts. However, this is contraindicated in certain conditions like diabetes mellitus, peptic ulcer and immunocompromised state[21,23,24]. Calcitonin act by inhibiting the calcitonin receptors that are present on giant cells thereby inhibiting osteoclastogenesis[17,25]. Interferons have anti-angiogenic effect and inhibition of bone resorption[1]. Nalan *et al*[26] have used the combination of surgical and medicinal treatment in their patient. Non surgical treatment options are simple, inexpensive, save vital structures and avoid facial deformity[2,23].

In conclusion, though the classic presentation of CGCG is a slow growing benign lesion in mandibular anterior region in a young patient, variable clinical appearances exist. Thus, it is still a topic of keen interest

to study about clarity in clinical behavior, radiographic features and various treatment modalities of this one of the bony lesion of jaws.

COMMENTS

Case characteristics

A 46 years old male had reported with a rapidly increasing intraoral and extraoral swelling of lower jaw following tooth extraction.

Clinical diagnosis

Extraorally bony hard, non-tender swelling on lower right side of face and exophytic soft tissue growth from the residual socket intraorally.

Differential diagnosis

Provisional diagnosis was malignant tumor.

Laboratory diagnosis

Serum calcium, phosphorus, alkaline phosphates, and parathyroid hormone which were within normal limits. Thus, exclude the brown tumor of the hyperparathyroidism.

Imaging diagnosis

Lateral mandibular occlusal view and a panoramic radiograph showed single large multilocular radiolucent lesion having well defined periphery with predominant buccal and lingual expansion and thinned-out of cortical plates suggested benign tumor like ameloblastoma.

Pathological diagnosis

Biopsy showed highly cellular fibrous connective tissue stroma, which consisted of many plump fibroblasts, extravagated blood elements and numerous multinucleated giant cells. These features were diagnostic of central giant cell granuloma (CGCG).

Treatment

Surgery was chosen as a treatment of choice.

Related reports

Immunohistochemistry by cytokeratin expression and giant cells were found to be positive for cytokeratin which confirmed the diagnosis of CGCG.

Term explanation

An aggressive variety of CGCG which was augmented following extraction of teeth is described.

Experiences and lessons

The necessity of radiographic examination prior to extraction of teeth, and the importance of early histopathological examination, if extraction socket fails to heal should not be underestimated.

Peer-review

The case report shows some valuable information to understand the diagnosis and treatment for this disease in future. The manuscript is written well and organized reasonable.

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