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Angular Cheilitis - An Updated Overview of the Etiology, Diagnosis, and Management

Research Article

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Abstract

Angular cheilitis (AC) is a common clinical entity which was described over a millennium ago. It is an inflammatory condition typified by erythema, moist maceration, ulceration, and crusting at the commissures of the mouth. The etiology of AC is quite diverse and notoriously difficult to pin down as it is construed to be a multifactorial disorder of infectious origin. Consequently, manifold local and systemic causes are implicated in the etiopathogenesis of AC. While considering local etiology; any factor that creates a chronic and moist environment for microbial growth at the oral commissures can be culpable in the etiology of AC such as habitual lip licking, thumb sucking or biting the corners of the mouth, reduced vertical height of the face, and sagging of tissues at the angles of the mouth, to name a few. Nutritional deficiencies namely iron, and members of the vitamin B family (riboflavin, pyridoxine, cobalamin, and niacin,) are established causative agents of AC. Although most of the time, AC could be a straightforward diagnosis, investigation into the exact etiology is critical. This is because AC could be the harbinger of more minacious systemic conditions such as Plummer Vinson syndrome, ulcerative colitis, Crohn's disease, orofacial granulomatosis, etc. Therefore, investigations into the actual etiopathogenesis are exigent to provide effective, felicitous adjunctive treatment in order to alleviate patient's discomfort and pain.

Keywords: Angular Cheilitis; Fungal Infection; Mixed Infection; Angular Stomatitis; Perlèche; Iron Deficiency Anemia.

Introduction

Angular cheilitis (AC) is an inflammatory lesion at the corners of the mouth which begins at the muco-cutaneous junction and extends to the skin [1]. It is also known as angular stomatitis, or "perlèche" which is derived from the French term "pourlècher" (to lick one's lips). AC is a relatively common lesion clinically characterized by erythema, moist maceration, ulceration, and crusting at the commissures of the mouth (Figures 1 & 2). Factors that create a chronic, conducive, moist environment for microbial growth at the oral commissures such as habitual lip licking, thumb sucking or biting the corners of the mouth, and sagging of tissues at the angles of the mouth have been implicated in the development of AC [2].

Angular cheilitis can be either unilateral or bilateral. They can present with soreness, pain, pruritus, or even burning sensation [1]. The occurrence is reported to be between 0.7-3.8% of oral mucosal lesions in adults and between 0.2-15.1% in children.It is seen predominantly in adults, equally in both males and females, and most commonly in their third to sixth decades of life [3]. In 1986, Ohman et al [4] classified AC into four basic types depending on the depth and number of rhagades (folds). Type I lesions are characterized by a single rhagade limited to the corner of the mouth while Type II lesions are more extensive in depth and length than type I lesions. Type III lesions show several rhagades radiating from the angle of the mouth into the adjacent skin with limited redness restricted to the vicinity of the rhagades. Type IV lesions exhibit extensive erythema of the skin adjacent to the vermilion border without the presence of rhagades. Dentate patients usually exhibit type I lesions more frequently and edentu-

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Figure 1. A case of angular cheilitis associated with nickel allergy in a patient undergoing orthodontic treatment.

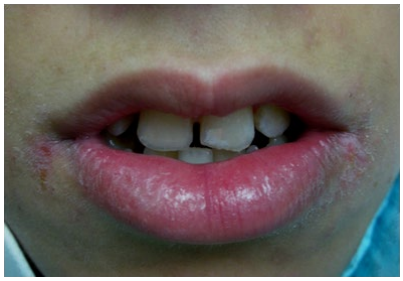
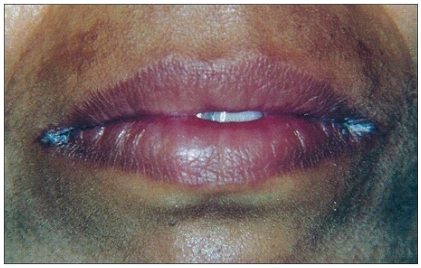


Figure 2. Angular cheilitis in an elderly patient secondary to xerostomia.



lous patients tend to manifest the other types. The cause of AC is multifactorial, and this brief review intends to discuss the various etiological factors, differential diagnosis, and treatment options of this condition.

Etiologic Factors

The cause of AC is multifactorial and could range from local etiologies to systemic ones. The local etiologies implicated in the development of AC can be classified under anatomical, mechanical, allergic, chemical, and infectious categories. These local factors can either act alone or combine with one another in developing the lesion. The systemic causes include nutritional deficiencies, systemic diseases, and drug-related side effects [3, 5].

Local Etiologies

Anatomical and physical causes: The most commonly reported local etiology that falls under the anatomical category is reduced or loss of vertical dimension of the jaws which would lead to overclosure of the mouth. This could be due to edentulousness and tooth migration among others. Weight loss in some patients could cause loss of facial elastic tissue, skin turgor, and reduce the vertical dimension of the facial structures.Reduction in the vertical dimension of the face causes pooling and stasis of saliva at the commissures of the mouth and eventual maceration of the skin and mucosa. Malnutrition, mouth breathing, and smoking have also been implicated in the reduction of facial height, stasis of saliva and causing AC [3]. The enzymes present in saliva such as amylase, maltase, lipase, catalase, sulfatase, hexokinase, carbonic anhydrase and others can cause digestion, irritation, and inflammation of the tissues at the angles of the mouth [6]. Trauma to the region in the form of ill-fitting orthodontic appliances, habitual lip licking or picking, thermal burns, denture cleaners, dental flossing, and iatrogenic causes can all irritate the commissures and cause inflammation [7, 8].

Allergic and Chemical Cause: Contact dermatitis can accentuate an already existing AC. In the presence of a potential allergen, the compromised mucosal barrier of AC allows easy penetration of the offender, and can thus aggravate the lesion [9]. This is commonly seen in nickel sensitive patients wearing orthodontic appliances or cast metal dentures containing nickel (Fig.1) [10]. Components of dental restorations, bridges, and retainers such as gold, mercury, palladium, potassium dichromate, cobalt, and others have been reported to cause allergic reactions and cause AC clinically. Flavoring and fragrance enhancing agents like cinnamic aldehyde, eugenol, spearmint oil, peppermint, menthol, carvone, propolis, mint essence, present in lipsticks, chewing gums, tooth pastes, cigarettes and oral hygiene products among others, have also been implicated in the development of AC as a consequence of an allergic reaction [7].

Microbial Causes: Pooling and stasis of saliva at the commissures of the mouth creates a chronic, conducive, and moist environment for microbial growth at these regions. This microbial growth can cause infection and clinically manifest as AC [3, 5]. Candida albicans, Staphylococcus aureus, and/or β-hemolytic streptococci are the most common culprits among microbial agents in causing AC [11]. Microbiologic studies have indicated that 20% of AC are caused by C. albicans alone, 60% are due to a combined infection with C. albicans and Staphylococcus aureus, and 20% are associated with S. aureusalone [11]. It is commonly seen in the elderly and immunocompromised patients especially HIV infected and AIDS patients [12, 13]. In a comparative study, Candida albicans and Staphylococcus aureus were found to be more prevalent in AC lesions of HIV seropositive patients, than that of HIV seronegative patients. Incidentally, in HIV seropositive patients with CD4 cell count less than 200 there was an increase in the incidence of Candidal and Staphylococcus aureus colonization when compared to patients with CD4 cell count higher than 200 (2). Multifocal candidiasis could manifest as AC as a part of its wide clinical spectrum.[8, 14]Fulminant systemic candidiasis can also involve the angles of the mouth and present clinically as AC [7].

Systemic Etiologies

Nutritional Causes: Nutritional deficiency is another widely studied etiological factor in the development of AC. Various nu-

tritional deficiencies have been implicated in the development of AC. The most significant among these are deficiencies of iron and some vitamins belonging to the B complex group [5].

Iron deficiency: Rose A John in 1968 proposed that iron deficiency status predisposes to the development of AC, with or without clinical manifestations of anemia. Low plasma iron concentration could impair the synthesis of iron-containing enzymes such as cytochrome oxidase, catalase, and peroxidase. This would impair cellular functions and their multiplication. Since epithelial cells undergo rapid turnover, they would be affected quite early owing to the decreased proliferation especially at the corners of the mouth, resulting in atrophic epithelium. This atrophic epithelium could be eroded easily and become conducive for the development of AC by overgrowth and colonization of normal oral flora like Candida, Staphylococcus, and Streptococcus. In patients with low plasma iron without clinical manifestations of anemia, angular cheilitis treatment with iron without thorough investigations could be crucial as more sinister cause such as gastrointestinal carcinoma or other underlying disease causing chronic blood loss could be overlooked [15].

In iron deficiency anemia, levels of an iron-binding protein called transferrin are reduced. Transferrin has fungistatic properties and its depletion or reduction in serum could predispose to the overgrowth of Candida in the oral cavity thus promoting Candidal infection and AC. Atrophy and hyperkeratinisation of the oral epithelium is seen in iron-deficiency anemia status. The atrophic epithelium is conducive for microbial growth while the hyperkeratinisation is a favourable environment for Candidal growth. [14].

Vitamin B complex deficiencies: Vitamin B complex is a class of water-soluble vitamins, that plays important roles in cell metabolism, and comprises of six main vitamins. The commonly reported vitamin deficiencies of the B complex group are riboflavin (B2), pyridoxine (B6), niacin (B3), cyanocobalamin (B12), folate (B9), and biotin (vitamin BW or vitamin H) [16].

Ariboflavinosis (chronic deficiency of riboflavin (B2)) can manifest clinically as angular cheilitis, glossitis, sore throat, and swelling and erythema of the oral mucosa. Concomitant normocytic, normochromic anemia and seborrheic dermatitis may also be present. Certain anti tuberculosis drugs like isoniazid are pyridoxine (B6) antagonists. Hence patients undergoing long term anti tuberculosis treatment may have deficiency of B6. Oral manifestations of pyridoxine deficiency may occur in the form of glossitis and cheilitis. This clinical picture is clinically identical to that observed in niacin deficiency state (pellagra) [16].

Cyanocobalamin (B12), also known as extrinsic factor, is essential for the production of erythrocytes. A glycoprotein known as intrinsic factor facilitates its absorption in the duodenum. In the absence of either cyanocobalamin or the intrinsic factor, production of RBCs can be affected and result in anemia. Oral mucosal barrier is compromised in anemic status and can predispose to the development of AC [14, 17].

Folic acid has been studied extensively in the development of AC [18, 19]. Absorption of folate is affected by oral contraceptives, phenobarbital, and many other drugs. Folic acid deficiency can sometimes be seen in combination with cyanocobalamin deficiency and present as AC among other oral mucosal findings. Folic acid deficiency is also known to cause burning mouth syndrome associated with angular cheilitis and glossodynia [19]. Biotin deficiency has been reported to be associated with AC. Dry eyes and alopecia are other clinical manifestations of biotin deficiency [20].

Systemic diseases: Many systemic causes have been reported to manifest AC. One of the most important systemic causes is xerostomia. This condition accounts for about 5% of cases diagnosed with AC [3]. This subjective feeling of dryness of the oral mucosa, has been reported as a complaint in one third of diabetic patients [21]. Other systemic causes of xerostomia would include salivary gland disorders, head and neck radiation therapy, chemotherapy, autoimmune diseases like Sjogren's syndrome, systemic lupus erythematosus, inflammatory bowel diseases like Crohn's disease and ulcerative colitis, and dehydration, among others. Xerostomia can be physiological when it is seen in the elderly as a part of the aging process, due to acinar and ductal atrophy (Fig.2). In these patients there could be an associated taste disorder, burning mouth syndrome, dental caries, and exacerbation of an existing AC [22, 23]. Xerostomia is also a common side effect of numerous medications. Over 500 drugs have been implicated to cause xerostomia as a side effect. Most cited ones among them are antihistamines like diphenhydramine, chlorpheniramine, and decongestants like pseudoephedrine. Other drug categories that may cause xerostomia are antidepressants, antipsychotics, sedatives and anxiolytic agents, antihypertensives, anticholinergics, etc. [24].

AC can be seen in cases of malnutrition, and eating disorders such as anorexia nervosa, and bulimia. These are most likely to be related to the nutritional deficiencies seen in these disorders [25]. AC has been reported as one of the common oral manifestations of systemic infectious diseases such as human immunodeficiency virus (HIV) infection and syphilis [5]. In HIV infection, oral mucosal lesions are an integral part of the clinical criteria in a number of classification systems. These classifications are based on the etiological factors or the strength/intensity of their association. AC is classified as an oral lesion strongly associated with HIV/AIDS infection and the etiology in these cases is mostly Candidal infection or mixed infection of Candida and Staphylococcus [26]. Patients with CD count <200 have been reported to have AC of the mixed infectious origin than Candida [2]. The prevalence of AC in HIV/AIDS is about 5.6% to 28.9% and it is reported to be the most common oral manifestation of HIV in children [13, 27]. Secondary syphilis often presents with split papules at the corners of the mouth and presents as AC, along with other dermatological manifestations. These are infectious and painful lesions, and harbor the causative treponemal organisms [28].

AC is a frequent manifestation in diabetes mellitus (DM). DM is an endocrine disease affecting multiple organs and xerostomia is one of the common oral findings in diabetics. It has been demonstrated that, due to higher blood glucose concentration, Candidal species may present higher hemolytic and esterase enzymatic activity in diabetic patients. This may contribute to increased enzyme activity and the Candidal species may be more pathognomonic in these patients. A localized immune suppression may disturb the homeostasis of the oral microflora, contributing further to the growth of pathognomonic fungal organisms. Candida, has been frequently isolated from the oral cavity of patients with DM. Up to 77% of insulin-treated diabetic patients are reported to be car-

riers of oral Candida and are susceptible to oral candidiasis [29].

Inflammatory bowel diseases such as ulcerative colitis and Crohn's disease may exhibit oral manifestations in the form of aphthous ulcers, fissures, glossitis, and AC. In a study by Lisciandrano et al., [30] the frequency of occurrence of AC in Crohn's disease has been reported to be 7.8%, while that in ulcerative colitis is 5%.Discoid lupus erythematous (DLE), an autoimmune disease affecting the skin, may also manifest cheilitis in the form of AC, among other dermatological and oral findings. About 18% of patients with DLE have been reported to exhibit AC [30, 31]. Uremic stomatitis is a complication of chronic renal failure. In uremic stomatitis AC may be an initial clinical sign before the other oral mucosal sites are affected. The oral lesions including AC could be the result of the breakdown of excessive urea present in the saliva of these patients by the oral bacteria and liberation of ammonia [32].

Pharmacological Agents: Certain pharmacological agents have been implicated in the etiopathogenesis of AC. Among them, paroxetine, a selective serotonin reuptake inhibitor, which is prescribed for anxiety and depressive disorders, has been often implicated in the development of AC [33]. In patients receiving long-term tetracycline therapy, AC has been commonly found [34]. Metronidazole, an antiprotozoal drug, with broad spectrum activity against anaerobic protozoa and microaerophillic bacteria, was reported to cause AC along with aphthous stomatitis.[35] In few other cases, isotretinoin has been implicated in the development of AC and has been used as an indicator of the toxicity level of the drug [36]. An anti-psoriatic drug called secukinumab, a known suppressor of keratinocyte proliferation and differentiation, caused recalcitrant forms of AC [37]. Other drugs that have been known to cause AC are warfarin, vinca alkaloids, methylprednisolone and dexamethasone, statins, benzodiazepines, felodipin, carbamazepine, cyclosporine and digoxin [38].

Differential Diagnosis

Any condition that causes xerostomia must be considered in the differential diagnosis. A clinically significant differential diagnosis to be taken into account while treating AC is herpes simplex infection. Herpes labialis lesions start as macules and become vesicular and then pustular. These pustules eventually rupture forming crusts. If these crusts are present at the commissures of the mouth, they would resemble AC. However herpetic lesions tend to be unilateral, and a history of preceding fluid-filled vesicle formation would be useful in the diagnosis of herpetic lesions [39]. Secondary syphilis (syphilitic papule), erosive oral lichen planus or lichenoid oral lesions, impetigo, atopic dermatitis, seborrheic dermatitis, allergic contact cheilitis, irritant contact cheilitis, early or isolated diffuse cheilitis, actinic cheilitis, cheilitis glandularis, cheilitis granulomatosa, and exfoliative cheilitis are to be considered in the differential diagnosis of AC [38].

Management Of Angular Cheilitis

Treatment of AC would begin with the identification of the cause. Infective, non-infective, allergic, and combination of these causes should be identified and treated accordingly (Table.1). Infective lesions would typically respond to antifungals, antiseptics, or combinations of both. When lesions do not respond to these antimicrobials, other etiological factors must be considered. Ill-fitting dentures and other dental appliances must be reconstructed to restore functionality and facial contour. In older patients with dentures, supportive care including management of dentures may be necessary. Improvement in denture fit or fabrication of newer ones to improve the vertical facial height may be needed. Topical application of petrolatum jelly, emollients, or lip balm is effective

Table 1. Summary of the local etiologies and their management.

Etiology	Probable causes	Management
Anatomical or Physical	Reduced or loss of vertical dimension of the jaws	improve the vertical facial height by newer dentures or fillers
	Excessive drooling	Anti-drooling prosthetic devices
	Habitual lip licking or picking	Habit cessation, avoid trauma
	Thermal burns	Prevention
	Denture cleaners	Rinses
	Dental flossing	Proper flossing instruction
	Ill-fitting orthodontic appliances	Proper fitting appliances
Allergic and chemical	Nickel containing appliances and dentures	Switch to alternative nickel-free materials like stainless steel, titanium, ceramic, etc.
	gold, mercury, palladium, potassium dichromate, cobalt containing dental components	Switch to alternative allergen free materials
	Flavouring and fragrance enhancing agents like cinnamic aldehyde, eugenol, spearmint oil, peppermint, menthol, carvone, propolis, mint essence, present in lipsticks, chewing gums, toothpastes, cigarettes, and oral hygiene products	Avoid allergen containing products
Microbial causes	Candida albicans	Topical application of nystatin, amphotericin B, ketoconazole, and miconazole nitrate
	Staphylococcus aureus	Topical application of mupirocin or fusidic acid
	β-hemolytic streptococci	Topical application of mupirocin or fusidic acid

as a barrier to reduce the maceration of the commissures and induce healing. Anti-drooling prosthetic devices in severe drooling cases such as a cannula incorporated into the dentures can channel salivary flow into the oropharynx, and photodynamic therapy using photosensitizers and diode light in non-responsive cases have been tried with some success [40, 41]. In some cases, to prevent the pooling of saliva due to loss of skin turgor, injectable fillers and surgical implants can be considered [38]. Patients must be advised on denture hygiene such as removal of dentures at night and cleansing them well before reinsertion in the morning [8]. Chewing gum containing xylitol, or chlorhexidine acetate/xylitol, may reduce AC in older patients by improving salivation [42]. Xerostomia in geriatric patients predisposes them to oral candidiasis which may manifest as AC. In these patients, periodic professional oral hygiene procedures and good oral hygiene are crucial to reduce the risk of oral candidiasis [43]. Elimination of behavioral habits that contribute to the development of AC such a lip biting, tobacco smoking must be encouraged.

Local application of antifungals, such as nystatin, amphotericin B, ketoconazole, and miconazole nitrate, seems to be a popular choice among clinicians for the treatment of infective AC. Nystatin 100,000 units/mL ointment topically twice daily, or gentian violet solution topically two to three times a day is effective in many cases. Alternatively, ketoconazole 2% cream topically, clotrimazole 1% cream topically, miconazole 2% cream topically are good treatment options [38]. When a mixed infection is suspected, then topical treatment with a combination of mupirocin or fusidic acid and 1% hydrocortisone cream could be effective [44]. One group found immense success in the treatment of AC with a combination of 1% isoconazole nitrate (ISN) and 0.1% diflucortolone valerate (DFV) ointment. This was because of the broad-spectrum action of ISN against many species of dermatophytes and bacteria, and the anti-inflammatory properties of DFV [45]. However, when antimicrobials and local management strategies fail, systemic causes may need to be investigated. These systemic causes could be in the form of nutritional deficiencies or systemic illnesses, or both. In Plummer Vinson syndrome (a form of iron deficiency), AC could be a presenting sign [46].

Conclusion

Angular cheilitis may appear in multitudinous forms. Even though, AC is widely considered as a multifactorial disorder of infectious origin, this does not necessarily imply that microbial organisms initiated the lesion by invading the tissues at the corner of the mouth. The possibility of local pre-disposing factors triggering conditions that facilitate microbial invasion cannot be repudiated. Delving into the etiology of AC is imperative in effectively educing a treatment plan that works. A sound initial evaluation of local pre-disposing factors can go a long way in effectively grappling with this multifactorial disease. Since AC is usually diagnosed clinically, it is incumbent on the clinician to glean all the medical and dental history potentially pertinent to the condition. The health care provider (HCP) should be cognizant and alert to pick on the cues that may indicate the diagnosis of AC. This can go a long way in mapping an effective treatment plan for the patient. For example, when confronted with a child with organized AC with or without lip swelling, it is vital to consider the diagnosis of Crohn's Disease in the differentials. Follow up of patients with AC is recommended at 2 weeks for obvious reasons and would enable the HCP to evaluate the success/effectiveness of the treatment rendered.

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