World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(REVIEW ARTICLE)

Unusual upper lip swelling: A review and a case report of cheilitis landularis

Negar Salehi [1] and Arman Salehi [2,*] Mahsa Kalantari [3]

[1] *Department of Oral Medicine, School of Dentistry, Rafsanjan University of Medical Sciences, Rafsanjan, Iran.*

[2] *Department of Operative Dentistry, School of Dentistry, Rafsanjan University of Medical Sciences, Rafsanjan, Iran.*

[3] *Department of Oral and Maxillofacial Pathology, and Oral and Dental Diseases Research Center, Kerman Dental School, Kerman University of Medical Sciences, Kerman, Iran*

World Journal of Advanced Research and Reviews, 2023, 19(01), 181–187

Publication history: Received on 22 May 2023; revised on 01 July 2023; accepted on 03 July 2023 Article DOI: https://doi.org/10.30574/wjarr.2023.19.1.1287

Abstract

Cheilitis glandularis (CG) is a rare inflammatory condition characterized by chronic enlargement and inflammation of the minor salivary glands in the lip. This article provides a comprehensive review of CG, including its clinical features, subtypes, and potential predisposing factors. Additionally, a case report is presented to illustrate the diagnostic challenges and management strategies associated with this uncommon disorder.

CG primarily affects the lower lip, leading to symptoms such as lip swelling, persistent inflammation, dryness, and ulceration. While the exact etiology remains elusive, factors such as infections, obstructions, and autoimmune processes are believed to play a role in CG development. Although the exact relationship is not well-established, stress and psychological factors may influence immune functioning and contribute to the exacerbation or recurrence of inflammatory conditions, including CG. The case report highlights an unusual upper lip swelling that was diagnosed as CG. This underscores the importance of thorough clinical examination, differential diagnosis, and histopathological evaluation in accurately identifying CG. Timely recognition and appropriate management are essential for optimizing patient outcomes and preventing potential complications. In conclusion, CG presents a diagnostic challenge due to its diverse clinical presentation. Clinicians should maintain a high index of suspicion when encountering lip swelling and consider CG in the differential diagnosis. Further research is needed to elucidate the underlying mechanisms and potential predisposing factors associated with CG, including the role of mental health. Increased awareness and understanding of this condition will facilitate early detection, appropriate management, and improved outcomes for individuals affected by CG.

Keywords: Swelling; lip; Cheilitis glandularis; Inflammation; Review

1. Introduction

Encountering cases with lip swelling in the clinic is not uncommon; however, its diagnosis and management is challenging for dentists and requires a thorough systemic examination and taking a complete history of the patient.

Swelling in the lips occurs in two ways: localized and diffused. Localized swelling in the lips usually occurs following trauma, cyst or tumor in the area, but diffused swelling in one or both lips are caused by an underlying condition or disease and can be one of the first clinical manifestations of a systemic disease. Therefore, it is necessary to know the conditions that cause this disorder.

Cheilitis Glandularis (CG) is an uncommon and chronic inflammatory disorder that involves the sub-salivary glands and leads to the dilation of the ducts of the glands, followed by the secretion of thick saliva from the ducts(1). The exact etiology of this disease is still unclear, although a number of reports have suggested sunlight, smoking, poor oral hygiene, weak immune system, and mental disorders as predisposing factors(2). It commonly affects the lower lip, but

* Corresponding author: Arman Salehi

there are also reports of other parts of the mouth being affected, including the lips, buccal mucosa, upper lip, and hard palate. When any area of the mucosa except the lips is involved, the term "stomatitis glandularis" is used(3). Differential diagnoses of disease include foreign body reaction, multiple mucocele, chronic sialadentitis of the minor salivary glands, granulomatous disease, factitious cheilitis, angioedema, and the beginning of malignant tumors of the glands(1). There are reports of the progression of the disease to squamous cell carcinoma. The treatment of choice in most cases is the removal of predisposing factors and conservative treatments such as intralesional corticosteroid injection and systemic use of antihistamines and antibiotics(2). In this paper, we discuss a review of lip swelling with regard to CG and also a case report.

1.1. CG Etiology

The etiology of granulomatous cheilitis is unknown, although various theories, such as syphilis (4), mental disorders (5), exposure to sunlight for a long time (6), chemicals, genetic disorders and family history, poor oral hygiene (7), smoking (8) and compromised immune system may play a role in the development of the disease.

1.2. Main clinical symptoms

CG may occur as a separate disorder or as part of other granulomatous diseases, such as Melkersson-Rosenthal syndrome, Crohn's disease and sarcoidosis although the following symptoms may be observed:

- Swelling and enlargement of the lower lip: The affected lip may appear swollen, thickened, and enlarged. This is due to the hypertrophy (increased size) of the minor salivary glands.
- Persistent lip inflammation: Cheilitis glandularis often presents as chronic inflammation of the lip, leading to redness, tenderness, and discomfort. The inflammation can be localized or involve a larger area of the lip.
- Persistent lip dryness and cracking: The chronic inflammation can result in dryness and fissuring of the lip, leading to pain, discomfort, and sometimes bleeding. Crust formation may also be observed.
- Mucous discharge: In some cases, cheilitis glandularis may be associated with the production of a mucous or clear discharge from the affected lip. This can be due to the excessive secretion of saliva by the enlarged salivary glands.
- Ulceration and erosion: Prolonged inflammation and trauma to the lip may result in the formation of ulcers or erosions. These can be painful and may contribute to further complications (9).

1.3. CG subtypes

CG can be classified into different subtypes based on the specific characteristics and histological findings. The subtypes of CG include (8):

- Superficial CG: This subtype is characterized by inflammation and enlargement of the minor salivary glands near the surface of the lip. It typically presents with redness, swelling, and superficial ulcerations or erosions.
- Deep CG: Deep CG involves inflammation and hypertrophy of the deeper minor salivary glands within the lip. It may manifest as a firm, submucosal swelling or nodular mass beneath the surface of the lip.
- Mixed CG: Mixed CG refers to a combination of superficial and deep CG features. It involves both the superficial and deep layers of the lip, resulting in a complex presentation with various clinical and histological findings.
- Actinic CG: Actinic CG is associated with long-term sun exposure and is often seen in individuals with a history of chronic sun damage to the lip. It may present with a thickened, dry, and scaly lower lip, along with the characteristic glandular changes.

These subtypes reflect different levels and patterns of involvement of the minor salivary glands within the lip. The diagnosis of CG and its specific subtype is typically made based on clinical examination, histopathological evaluation of a biopsy sample, and sometimes additional imaging studies. Treatment approaches may vary depending on the subtype and severity of the condition, and they may include topical therapies, systemic medications, or in some cases, surgical intervention. It is recommended to consult with a dermatologist or oral medicine specialist for an accurate diagnosis and appropriate management.

1.4. CG prevalence

CG is almost uncommon, impacting approximately 0.08% of the community. It involves male and female equally. Less prevalent in certain breeds. Several studies suggest that it is more common in adolescent, although others reveal that it could occur at any age(10).

2. Case report

The patient is a 26-year-old woman who first presented 3 years ago with a complaint of recurrent upper lip swelling. Accordingly, the swelling first appeared a year ago, and after that, numerous blisters appeared on the lips, and within two weeks, the swelling gradually decreased until it was completely resolved. This situation has been repeated every four months. For the first time, a bruise appeared in the upper lip area after swelling (Figure 1A), which has not been resolved. In the biopsy performed from the area of the minor salivary glands in the upper lip, after Hematoxylin and Eosin staining, the infiltration of lymphocytes in the minor salivary glands as well as the infiltration of lymphocytes and neutrophils in the sub-epithelial layer are observed (Figure 1B). The patient visited a dermatologist several times for treatment and was diagnosed with recurrent herpes labialis and was treated with Acyclovir tablets and ointment, but there was no improvement.

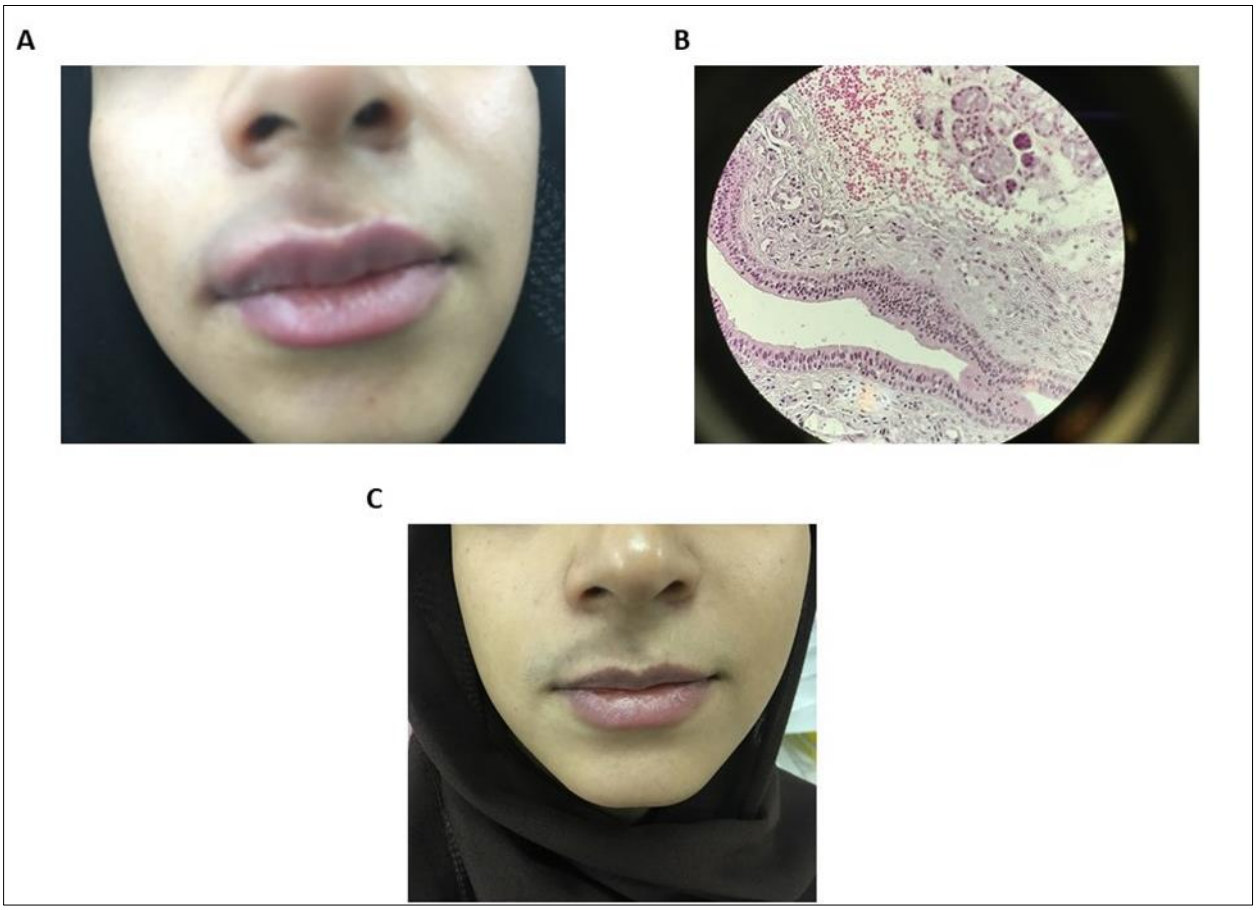

Figure 1 (A) Swelling and discoloration of the upper lip in the first session of the patient's visit. (B) The infiltration of lymphocytes in the minor salivary glands as well as the infiltration of lymphocytes and neutrophils in the sub-epithelial layer are observed in Hematoxylin and Eosin staining. (C) Cheilitis glandularis in the upper lip, four months after the start of the treatment, the swelling in the mentioned area has disappeared and there was no recurrence during the treatment

Therefore, after one year of unsuccessful treatment, he came to us with a complaint of recurrent swelling of the upper lip, which was last created three days ago. In the clinical examination, diffused swelling of the upper lip with a firm consistency was seen, there was no induration and tenderness on touch, and no ulcer or any other abnormal lesions were observed in the labial mucosa, and thick saliva or pus did not come out of the minor salivary glands of the lip with gentle pressure on the lip. A large purple macule was observed unilaterally on the right side of the upper lip, and the diascopy test was negative. There was no history of allergy or injection in the lip neither for therapeutic nor for aesthetic purposes. No lymphadenopathy was observed in the examination of the lymph nodes, and there were reports of abdominal cramps, weight loss, and frequent colds in the systemic examinations. The patient has severe anxiety and depression since two years ago, does not mention smoking history and has good oral hygiene. According to the symptoms of the patient with the primary diagnosis of granulomatous disorder (including Crohn disease, Wegner disease, Sarcoidosis, granulomatous cheilitis, orofacial granulomatosis, etc.) and differential diagnoses of vascular

maformation, hereditary angioedema (C1 esterase inhibitor deficiency) and CG from a deep incisional biopsy of the labial mucosa of the upper lip was performed and CBC/ESR, ANA, PANCA, CANCA, Ca, ACE, ANA and Calprotectin tests were requested. MRI of the upper lip was also requested to rule out vascular malformations, but the patient did not agree to do it. Abnormalities were not observed as a result of laboratory tests. Hematoxylin and Eosin staining of the sample showed scattered infiltration of lymphocytes and neutrophils in the subepithelial layer, also in the sub-salivary glands, lymphocyte infiltration was observed, although no granuloma was seen in the microscopic examination of the sample. The histopathological characteristics were suggestive of CG, therefore, with this final diagnosis, the patient was treated in such a way that triamcinolone injection was performed in the patient's lip and this monthly injection continued for 4 months. There was no recurrence of the lesion during the treatment, and no recurrence was observed in the one-year follow-up of the patient (Figure 1C). The patient was referred to a dermatologist for the purple color change on the upper lip and was treated. In the one-year follow-up of the patient, this color change had also faded.

2.1. Differential Diagnosis and Considered Disorders

Among the disorders considered in the differential diagnosis were lesions originating from the small salivary glands, both of infectious origin (odontogenic/nonodontogenic) and mesenchymal tumors with vascular, smooth muscle, or neural origins. Mucoceles or salivary duct cysts are commonly observed swellings involving the lips due to the abundance of small salivary gland tissue and the likelihood of unintentional damage. Typically, they present as hard, blue nodular swellings. The surrounding mucosa often shows scarring due to repeated unintentional rupturing of the cysts. Partial obstruction of the salivary ducts by sialolith stones can also cause local soft tissue swelling. It has been noted that mucoceles are almost exclusively found on the lower lip and rarely on the upper lip. The possibility of the bump being a mucinous tumor was ruled out based on the normal upper mucosa and the absence of a history of lip trauma (11).

Small salivary gland tumors account for about 10-15% of all salivary gland tumors and are commonly found on the roof of the mouth and lips (12). Salivary gland tumors affecting the accessory salivary glands of the lip primarily occur on the upper lip, with occasional cases on the lower lip. The development of these tumors is generally not associated with trauma or injury to the lip. Approximately 75% of salivary gland tumors of the upper lip are benign, with polymorphic and ductal adenomas being the most prevalent. Polymorphic adenomas are more frequent in adolescents, and the lip is the most common location for tubular adenomas. The clinical findings in this case suggest that it is most likely a small benign salivary gland tumor (13).

Hemangiomas typically present in infancy and childhood, characterized by a rapid proliferative phase followed by gradual regression. Superficial lesions are usually reddish-bluish in color and have ill-defined borders. They easily compress and slowly refill when released. However, the short duration of the lesion, non-compressibility, lack of blanching, and the age of the patient make the diagnosis challenging.

Persistent lip artery, also known as pulsating upper lip, is more common in the elderly and is often associated with other vascular lesions such as hemangiomas, arteriovenous malformations, and varicose veins (4). It is frequently misdiagnosed as a salivary duct cyst, and cases of heavy bleeding during surgical removal have been reported.

Lymphangioma, a benign hyperplasia of the lymphatic vessels, most commonly occurs on the tongue but can also affect the roof of the mouth, oral mucosa, gums, and lips. It presents as a painless, asymmetrical nodule. In rare cases, it can cause diffuse, symmetrical enlargement of the lips. The diagnosis of lip tissue infection (dental/nonodontogenic) is not justified in this case due to the long duration of the lesion, the absence of symptoms, and normal teeth. Abscesses that cause lip swelling are often painful, erythematous, fluctuating, and poorly defined. Smooth muscle tumors, typically benign, are uncommon in the oral cavity. This rarity can be attributed to the limited presence of smooth muscle in oral tissues, primarily found in the vascular walls and occasionally in the papillae surrounding the tongue (14). Most cases are detected along with the 3rd decade of life and are declared as a painless, slow-growing lesion. Since the lip is one of the most frequent sites, leukemia has been determined an available diagnosis. Reactive and neoplastic lesions were also considered (traumatic neuroma, neurofibromatosis, neuroblastoma). A traumatic neuroma, resulting from trauma or amputation, is not a true tumor but rather a regenerative response in an injured nerve trunk. In the context of oral trauma, a traumatic oral neuroma manifests as a small nodular growth near the neural foramen, lips, or tongue. When pressure is applied, it often elicits intense localized pain at the site (6). The case revealed no evidence of trauma, and remarkably, the swelling or lesion was completely painless.

Neurofibromas could represent as discrete, non-ulcerative nodules and have the identical color like normal mucosa (15). Although most prevalent in the head and neck part, excessive swelling or enlargement of the upper lip is considered to be highly uncommon.. Neurofibromatosis is another common tumor of the peripheral nerve sheath,

involving Schwann cells, perinerve cells, and endothelial fibroblasts mixture. It is considered a single lesion or component of the systemic syndrome of neurofibromatosis. There are no differences between the two variants, except for the lack of systemic and genetic aspects in the solitary form (15). Disorders including orofacial granulomatosis (Markerson-Rosenthal syndrome, granulomatous cheilitis), Crohn's disease, sarcoidosis, mycobacterial infections (tuberculosis, leprosy), among others, can result in hypertrophy of orofacial tissues, including the lips (7, 16). This lip swelling is generally dispersed in nature and has a long background of regression and repetition. Bilabial involvement associated with other systems such as the gastrointestinal tract is more frequent. Other disorders, such as angioedema, contact allergy, and cheilitis gland, are typically associated with pathogens or genetic factors and can manifest as enlargement of the salivary glands of the lips, resulting in nodularity of the lips and inflamed ductal orifices of the lip mucosa. Given the distinct nature of the lesion, its short duration, and the absence of exposure to known pathogens, the diagnosis of granulomatous/nongranulomatous swelling of the upper lip is not supported (17).

2.2. Suggested treatments

There is no definite medication to cure CG. Corticosteroids are the most accepted treatment to help diminish swelling and avoid frequent recurrences (relapses). Based on the severity, the doctor may recommend corticosteroids in the form of creams, tablets, or injections. However, there are some medications that could be advised:

- Intralesional corticosteroid injections such as triamcinolone acetonide or betamethasone dipropionate and sodium phosphate retard are prescribed as the first phase of treatment. 3-6 Intralesional injection may be used.
- Systemic corticosteroids such as prednisone 30-40 mg/day for about 2-3 weeks and then gradually reducing the drug over 1-3 months can cause significant improvement of the lesion.
- Minocycline 100-200 mg/day for 3-6 months in combination with systemic corticosteroid is the best treatment regimen.
- clofazimine, thalidomide, hydroxychloroquine; Sulfasalazine and dapsone are used as the second line of treatment.
- Plastic surgery is performed to reconstruct the deformed lip in advanced and chronic cases of lip deformity(1).

3. Discussion

Chronic swelling of the lips, which sometimes occurs repeatedly, is a controversial problem because it not only affects the daily function of the lips, but also can cause major deformities. Many local and systemic conditions play a role in creating this condition, including granulomatous disorders (Crohn disease, Sarcoidosis, Tuberculosis, Leprosy, Orofacial granulomatosis), deep fungal infections, CG, neoplasms (non Hodgkin lymphoma and,.etc.), hereditary angioedema, amyloidosis, lip cosmetic injections and the use of drugs such as cyclosporine.

The referring patient who came with symptoms of swelling, sores and bruises on the upper lip, was initially treated with the wrong diagnosis of herpes and after not responding to the usual herpes treatments, she referred to an oral disease specialist. In this situation, he was diagnosed with granulomatous disorder, CG, vascular malformation and hereditary angioedema.

CG usually occurs in old or middle-aged men and rarely affects women and children. In most cases of CG, the lower lip is affected, and in a few cases, the upper lip has been reported(18).

CG can be divided into three categories based on severity: 1) Simple: In this type of lesions, multiple painless lesions, dilated opening of ducts and numerous small palpable nodules can be observed. There is no inflammation, but the mucinous substance can come out by applying pressure on the lip. 2) Superficial suppurative (Baelz's disease): If the simple lesion becomes infected, it can cause the superfacial type, in this type of superficial wound, the crust is painless and swollen, characterized by the stiffness of the lip, and there is mucinous exudate at the entrance of the duct. 3) Deep suppurative (CG apostematosa): If the infection penetrates into deeper tissues, it can cause this type of CG, which can lead to abscesses and fistulas(19).

4. Conclusion

Cheilitis glandularis (CG) is a rare and intriguing condition characterized by chronic inflammation and enlargement of the minor salivary glands in the lip. This article provided a comprehensive review of CG, highlighting its clinical features, subtypes, and potential predisposing factors. Additionally, a case report was presented, underscoring the importance of early recognition and appropriate management of this uncommon disorder.

The review revealed that CG primarily affects the lower lip, leading to symptoms such as lip swelling, persistent inflammation, dryness, and ulceration. The subtypes of CG, including superficial, deep, mixed, and actinic, were discussed, showcasing the different levels and patterns of glandular involvement. While the exact etiology of CG remains elusive, it is believed to involve factors such as infections, obstructions, and autoimmune processes.

Interestingly, the potential role of mental disorders as predisposing factors for CG was explored, although further research is warranted to establish a direct link. Stress and psychological factors may influence the immune system and contribute to the exacerbation or recurrence of chronic inflammatory conditions, including CG.

The presented case report highlighted a patient with an unusual upper lip swelling that was ultimately diagnosed as CG. This underscores the importance of clinical examination, differential diagnosis, and histopathological evaluation in diagnosing CG accurately. Prompt identification and appropriate treatment are crucial in managing this condition and preventing potential complications.

In conclusion, CG is a rare condition that poses diagnostic challenges due to its varied clinical presentation. Clinicians should maintain a high index of suspicion when encountering unusual lip swelling and consider CG in the differential diagnosis. Further research is needed to elucidate the underlying mechanisms and potential predisposing factors associated with CG, including the role of mental health. Increasing awareness and understanding of this condition will facilitate early detection, appropriate management, and improved outcomes for individuals affected by CG.

Compliance with ethical standards

Acknowledgments

We would like to acknowledge Department of Operative Dentistry, School of Dentistry, Rafsanjan University of Medical Sciences, Rafsanjan, Iran.

Disclosure of conflict of interest

The authors declare no potential conflict of interest.

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