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ORIGINAL ARTICLE

Association between cheilitis granulomatosa and odontogenic infections: A case–control study

Xiaosheng Hu[1] | Yixiao Xing[1] | Changqing Mu[1,2] | Yang Liu[1] | Hong Hua[1]

[1]Department of Oral Medicine, Peking University School and Hospital of Stomatology, Beijing, China

[2]Department of Stomatology, Beijing Friendship Hospital, Capital Medical University, Beijing, China

Correspondence
Hong Hua and Yang Liu, Department of Oral Medicine, Peking University School and Hospital of Stomatology, 22 South Zhongguancun Avenue, Haidian District, Beijing 100081, China.
Emails: honghua1968@aliyun.com (H.H); shannon13579@163.com (Y.L.)

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Abstract

The association between cheilitis granulomatosa and dental infections (dental caries and apical periodontitis) is still not well understood. Herein, we aimed to investigate the association in large hospital cases with cohort controls. Cheilitis granulomatosa cases (n = 181) were retrieved from Peking University Hospital of Stomatology and age- and sex-matched to controls (n = 181). The χ^2-test, Student's *t*-test, and Mann–Whitney *U*-test were used to compare the differences between groups. The χ^2-test and odds ratio were used to verify if there was an association and risk relationship. The results showed that both dental caries and apical periodontitis were associated with cheilitis granulomatosa ($p < 0.001$). Individuals with cheilitis granulomatosa had approximately a twofold increased frequency of dental caries than those without cheilitis granulomatosa (104/181, 57.5% vs. 53/181, 29.3%) ($p < 0.001$). The odds ratio of dental caries occurring in the case group compared to the control group was 3.211. The frequency of apical periodontitis in patients with cheilitis granulomatosa was significantly greater than in those without cheilitis granulomatosa (109/181, 60.2% vs. 28/181, 15.5%) ($p < 0.001$). The odds ratio was 8.272. Moreover, apical periodontitis was also locationally related to cheilitis granulomatosa ($p < 0.001$). Collectively, our study showed that the foci of dental infections are associated with cheilitis granulomatosa, suggesting that proper treatment of focal teeth may be important in the management of cheilitis granulomatosa.

KEYWORDS
apical periodontitis, cheilitis granulomatosa, dental infections, Melkersson–Rosenthal syndrome, orofacial granulomatosis

1 | INTRODUCTION

Cheilitis granulomatosa (CG), first described by Miescher in 1945, is a cosmetically distressing and persistent idiopathic lip swelling. CG is a rare inflammatory disorder which is one of the manifestations of orofacial granulomatosis (OFG).[1] OFG is an uncommon chronic inflammatory disorder and is histopathologically characterized by subepithelial non-caseating granulomas. It typically affects the soft tissues of the orofacial region, but should exclude other known causes of granulomatous inflammation and systemic diseases, such as Crohn's disease (CD), sarcoidosis and mycobacterial infection.[2] Melkersson and Rosenthal[3] described the association between recurrent/chronic orofacial edema, facial palsy, and fissured tongue (lingua plicata) and proposed the term Melkersson–Rosenthal syndrome (MRS). CG can occur by itself or as part of the MRS. All in all, OFG encompasses a spectrum of known granulomatous diseases including localized lip swelling of granulomatous cheilitis and more extensive inflammation of MRS.[4]

Cheilitis granulomatosa can occur at any age, the first symptoms of CG usually appear in the second decade of life,[5,6] and it was

Xiaosheng Hu and Yixiao Xing have contributed equally to this work and share first authorship

prevalent in adults with peak incidence between 20 and 40 years of age.[4] CG has no predisposition to race, but has a female predilection.[7] The incidence of GC is estimated at 0.08% in the general population.[2]

So far, the etiology and pathogenesis of CG remain obscure. Hereditary, allergic, inflammatory, infectious, hypersensitivity, and microbial factors have been hypothesized but remain unproven. The involvement of the immune response triggered by microbial agents in the etiology of OFG has been suggested on the basis of microorganisms; especially, bacteria is associated with similar chronic granulomatous conditions, such as CD.[8] A previous study has showed that infectious agents, especially odontogenic foci of infection, may play a crucial role in the development of CG or MRS for good response following elimination of dental foci.[5]

Apical periodontitis (AP), defined as an inflammatory process related to the presence of infection caused by intraradicular microorganisms,[9] has drawn our attention because several reports showed that patients can recover or improve from the swelling of lips by treatment of AP.[10,11] Therefore, it is necessary to clarify whether the swelling of the lips is associated with AP in CG patients with AP. Apart from AP, other focal dental infection such as periodontitis, endodontic lesions, and dental caries are also worth exploring.[11–13]

However, to our best knowledge, all available literature thus far about the relationship between CG and dental infection are only case reports; large-sample clinical evidence is not available to support the speculation that odontogenic infection is associated with granulomatous lesions in CG, MRS, or OFG. Based on the case reports and owing to the scarcity of published work in case–control studies, we aimed to test the hypothesis that the development of CG is associated with odontogenic infections. Moreover, we explored whether there was a locational association between CG and odontogenic infections.

2 | METHODS

2.1 | Study design

This study followed the STROBE guidelines (Strengthening the Reporting of Observational Studies in Epidemiology). This observational hospital case–control study was retrospectively evaluated. As CG, MRS, and OFG all have focal non-necrotizing granulomas in lips and the study focused on labial granulomatous swelling, the cases in this study were obtained from patients diagnosed with CG, MRS, or OFG from January 2012 to June 2018 in the Department of Oral Medicine, Peking University Hospital of Stomatology. The age- and sex-matched control group comprised patients diagnosed with other oral diseases (oral lichen planus, chronic cheilitis, contact cheilitis, mucous cyst in lips, and recurrent aphthous ulcer) from January 2012 to June 2018 in the Department of Oral Medicine, Peking University Hospital of Stomatology.

2.2 | Ethical considerations

This study was approved by the Institutional Review Board of Peking University School and Hospital of Stomatology (PKUSSIRB-201627040) and all methods were performed in accordance with the relevant guidelines and regulations.

2.3 | Sample size estimation

Sample size was estimated via χ^2-test using $\alpha = 0.05$ and $\beta = 0.10$. A pilot study was carried out to estimate the sample size. Based on data from the pilot study, the proportion of untreated AP or dental caries among controls was 0.4, and that in cases was 0.62. The ratio between the cases and controls was set at 1:1. Thus, an estimated minimum sample size was set at 208 (104 cases and 104 controls).

2.4 | Diagnosis of CG, MRS, and OFG

Lip biopsy was performed on all of the cases included in the study and demonstrated with non-caseating granulomatous inflammation. In addition to the results of lip histological examination satisfying non-necrotizing granulomas, cases that satisfied the following requirements were diagnosed as OFG: (i) the presence of relevant orofacial clinical features (mainly labial enlargement, swellings of the perioral or periorbital tissues, and sometimes oral ulcers, buccal, and labial mucosal swelling, or gingival enlargement);[14] and (ii) the exclusion of systemic disorders (e.g. CD, sarcoidosis) causing similar manifestations through detailed medical history and serological, radiological, or endoscopic investigations (where clinically justified). Those with only lip swelling were diagnosed with CG and those with the full triad of manifestations (orofacial edema, facial palsy, and fissured tongue) were diagnosed with MRS.[1,4]

2.5 | Selection of cases and controls

The inclusion criteria for cases were as follows: (i) fulfilled the clinical and pathological diagnostic criteria for CG, MRS, or OFG; and (ii) had no history of maxillofacial surgery, radiotherapy, and chemotherapy. To ensure comparability, age- and sex-matched controls were randomly selected from patients who had been managed at the above hospital and diagnosed with other oral mucosal diseases in lips other than granulomatous disease between January 2012 and June 2018. The inclusion criteria for controls were as follows: (i) no systemic disorders (e.g., CD, sarcoidosis, and tuberculosis); and (ii) no history of maxillofacial surgery, radiotherapy, and chemotherapy. Ultimately, 362 participants (181 cases and 181 controls) were included in this hospital case–control study for the final analysis.

2.6 | Diagnosis of dental caries and AP

Dental caries and AP were recorded by clinical examination and radiographically diagnosed (periapical radiographs, panoramic radiographs, or computerized tomography). Caries or periapical disease was diagnosed by two general dentists, and the kappa agreement coefficient for the diagnosis was 0.75 or more. AP with or without fistulas were also recorded. Dental caries or AP after proper and complete tooth filling treatment or root canal therapy were not recorded.

2.7 | Data collection

Data extraction and collection were completed independently by the first authors (C.Q.M. and Y.X.X.). Disagreements were resolved through rechecks and discussion or consulting a third author (X.S.H. and H.H.). Basic information of patients and controls, including age, sex, and medical history, were collected. Records of oral examination were extracted, which included the number and position of dental caries and periapical diseases (except those lesions that had undergone complete medical treatment). For the case group, the conditions of the disease were extracted. The courses of swelling, the position of swollen lips (upper or lower lip), family history, pathological findings, former management, and physical examination were recorded.

2.8 | Statistical analysis

Characteristics of the variables were presented as mean ± standard deviation (SD) values for continuous variable (age) and as frequency distributions for categorical variables (all others; Table 1). Normally distributed continuous variables were compared using Student's *t*-test and discrete variables were compared using the χ^2-test. Mann–Whitney *U*-test was used when the sample data were not normally distributed. The χ^2-test and odds ratio test were used to verify any association and risk relationship between the occurrence of CG and dental infections. Statistical significance was set at $p < 0.05$. The data analysis was conducted by SPSS software version 21.0.

TABLE 1 Characteristics of CG cases and controls

Variables	Cases (n = 181)	Controls (n = 181)	*p* Value
Age, years	44.01 ± 14.68	44.01 ± 14.71	0.997 (t test)
Sex			
Male	85	85	1 (χ^2 test)
Female	96	96	
Smoking			
Yes	11	7	0.333 (χ^2 test)
No	170	174	
Alcohol intake			
Yes	19	21	0.737 (χ^2 test)
No	162	160	

Note: Data are shown as mean ± standard deviation.
Abbreviations: CG, cheilitis granulomatosa.

3 | RESULTS

3.1 | Characteristics of participants

This hospital case–control study consisted of 362 participants: 181 CG cases and 181 controls (Table 1). The controls included 54 cases of oral lichen planus (29.8%), 72 chronic cheilitis (39.8%), 12 contact cheilitis (6.6%), five mucous cyst in lips (2.8%), and 38 recurrent aphthous ulcer (21.0%). Smoking ($p = 0.333$) and alcohol intake ($p = 0.737$) were not different between the two groups. The conditions of oral hygiene in cases and controls were evaluated by using plaque index (PLI) and calculus index–simplified (CI-S), and the results showed that neither PLI ($p = 0.116$) nor CI-S ($p = 0.214$) was different between the two groups (Table S1).

3.2 | Characteristics of patients with CG

The course of disease before correct diagnosis ranged 0.5–240 months, and the mean period was 12 months. Of the patients, 60.2% were diagnosed within 12 months from the onset of lip swelling. The age of the case group ranged 6–80 years (median, 46; mean, 44.01 ± 14.68). More than 80% of patients in the case group (82.9%) were 20–60 years old and 76.2% of patients in the case group were 30–60 years age, and only 14.4% of the patients in case group were less than 30 years old. The mean age of the male and female patients was 39.84 ± 14.51 and 47.71 ± 13.88, respectively; female patients were older than male patients ($p < 0.001$). For the three subgroups, the mean age of the CG only group (subgroup 1) was 44.31 ± 14.61 years, of the MRS group (subgroup 2) 39.72 ± 15.93, and of the OFG group (subgroup 3) 47.61 ± 12.68. We did not find statistical differences in the mean ages among the three subgroups (Table 2). Fifty-seven (31.5%), 82 (45.3%), and 42 (23.2%) patients had swelling in the upper, lower, and both upper and lower lips, respectively (Table 2).

3.3 | Association between dental caries and CG

Overall, 77 of the 181 patients with CG had one or more caries (prevalence, 42.5%). For each subgroup in cases (CG only, OFG, and MRS), the number of patients with caries was 52, 13, and 12, respectively. The prevalence of caries in each subgroup was 43.0%, 40.6%, and 42.9%, respectively. No statistical differences were found in each subgroup. On the other hand, 53 of the 181 controls were found to have caries upon examination (prevalence, 29.3%). Significant differences were found between the two groups in the prevalence of

TABLE 2 Epidemiological information of patients with CG

	Cases with CG (n = 181)		
	CG only (n = 121)	MRS (n = 32)	OFG (*n* = 28)
Sex			
Male (n = 85)	65	13	7
Female (n = 96)	56	19	21
Age (in years)	44.31 ± 14.61	39.72 ± 15.93	47.61 ± 12.68
Age of male patients (39.83 ± 14.51)	40.49 ± 14.86	36.23 ± 14.32	40.43 ± 12.19
Age of female patients (47.71 ± 13.86)*	48.75 ± 13.09*	42.11 ± 16.89	50.00 ± 12.18
Position of swollen lips			
Upper lips (n = 57)	36	18	3
Lower lips (n = 82)	60	6	16
Both lips (n = 42)	25	8	9

Note.: Data are shown as mean ± standard deviation. *$p < 0.05$, age of male patients compared with female patients.

Abbreviations: CG, cheilitis granulomatosa; MRS, Melkersson–Rosenthal syndrome; OFG, orofacial granulomatosis.

TABLE 3 Occurrence of dental caries and AP in CG group and control group

Variable	Cases (n = 181)	Controls (n = 181)	Total
With caries	104	53	157
Without caries†	77	128	205
With AP	109	28	137
Without AP‡	72	153	225

Note: Data are displayed as number of patients. †$p < 0.001$, CG is associated with dental caries (OR = 3.211). ‡$p < 0.001$, CG is associated with AP (OR = 8.272).

Abbreviations: AP, apical periodontitis; CG, cheilitis granulomatosa; OR, odds ratio.

caries (Table 3). The odds ratio of dental caries occurring in the CG group compared to the control group was 3.211.

3.4 | Association between AP and CG

In the case group, we found that 109 had periapical lesions (prevalence, 60.2%). In all, 77 of subgroup 1, 13 of subgroup 2, and 19 in subgroup 3 were recorded with periapical lesions. The total number of teeth with periapical lesions was 281 (mean, 1.55). Among all cases with periapical lesions, 48 patients (33 in subgroup 1, seven in subgroup 2, and eight in subgroup 3) were recorded with 65 fistulas. In the control group, 28 of the 181 were recorded with periapical lesions, including eight with fistulas. The total number of teeth with periapical lesions was 58 (mean, 0.32). The prevalence of periapical lesions in the case group was statistically higher than that in the control group (Table 3). The odds ratio of AP occurring in the case group compared to the control group was 8.272.

3.5 | Locational association between odontogenic infections (caries or AP) and CG

A representative case of CG with AP is showed in Figure 1. Physical examination revealed diffuse swelling of the lower lip (Figure 1a). Histological examination of biopsy specimens from the lower lip revealed non-caseous epithelioid cell granulomas with inflammatory cell infiltrates (Figure 1c,d). Orthopantomography demonstrated apical radiolucency around the roots of right lower sixth molar teeth (Figure 1b).

To determine whether odontogenic infections located in the maxillary or mandibular areas and swelling located in the upper or lower lip are linked, we recorded and analyzed the locations of the lesions.

The relation of the caries location and that of the lip swelling were explored (Table 4) using the χ^2-test, and no relation was found to exist ($p > 0.05$).

The position of apical periapical lesions in the two groups was also recorded (Table 4). In the case group, of all patients with granulomatous upper lip swelling (including bilateral lips swelling), 48 had AP and 34 had maxillary AP (Table 5). There was a strong relation between granulomatous upper lip swelling and periapical lesions in the maxillary area (Table 5, $p < 0.001$). Similarly, in the case group, of all patients with granulomatous lower lip swelling (including bilateral lips swelling), 85 had AP and 75 had AP in the mandible (Table 5); diseases of the lower lip and lower jaw were highly correlated (Table 5, $p < 0.001$).

3.6 | Association of fistulas in AP with CG occurrence

Apical periodontitis with or without fistulas was also analyzed (Table 6). AP with fistulas was observed in 43% (47/109) of all the

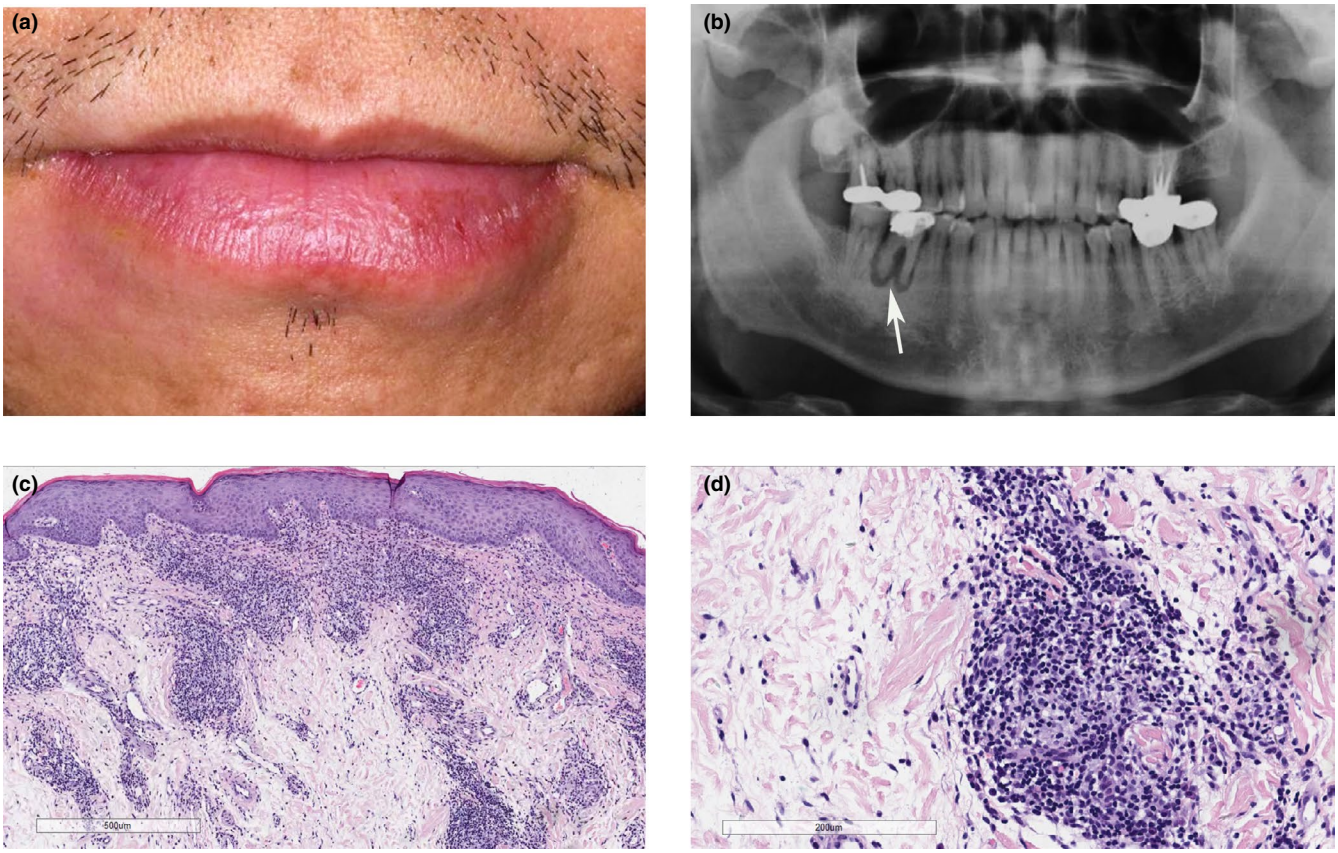

FIGURE 1 A representative case of cheilitis granulomatosa with apical periodontitis. (a) Diffuse swelling of the lower lip. (b) Roentgenogram of the lower and upper mandible reveals round translucent areas in the right lower sixth molar teeth (white arrow) which suggested apical periodontitis. (c) Biopsy specimen of the lower lip showing granulomatous inflammations focally distributed in the dermis (hematoxylin–eosin [HE], original magnification ×100). (d) Biopsy specimen of the lower lip showing non-caseating epithelioid cell granuloma (HE, ×200).

TABLE 4 Location of caries/AP and location of granulomatous lip swelling

	Caries			
Location	**Maxillary**	**Mandibular**	**Both**	**Total**
Swelling lips				
Upper	7	7	6	20
Lower	6	6	7	19
Both	10	3	7	20
Total	23	16	20	59
	AP			
Location	**Maxillary**	**Mandibular**	**Both**	**Total**
Swelling lips				
Upper	11	5	8	24
Lower	3	40	18	61
Both	7	9	8	24
Total	21	54	34	109

Note: Data are displayed as number of patients.

Abbreviations: AP, apical periodontitis.

TABLE 5 Association between granulomatous upper/lower lip swelling and periapical lesions in maxillary/mandibular

	Maxillary		
	With AP	Without AP	Total
Upper lip[†]			
With granulomatous swelling	34	14	48
Without granulomatous swelling	21	40	61
Total	55	54	109

	Mandibular		
	With AP	Without AP	Total
Lower lip[‡]			
With granulomatous swelling	75	10	85
Without granulomatous swelling	13	11	24
Total	88	21	109

Note: Data are displayed as number of patients. [†]$p < 0.001$, granulomatous upper swelling associated with AP in maxillary area. [‡]$p < 0.001$, granulomatous lower swelling associated with AP in mandibular area.

Abbreviation: AP, apical periodontitis.

AP in the case group and 18% (6/33) in the control group. The result showed that fistulas in AP were related to CG ($p = 0.009$).

TABLE 6 Occurrence of periapical fistula in CG group and control group

	Cases	Controls	Total
AP without fistulas	62	27	89
AP with fistulas*	47	6	53
Total	109	33	142

Note: Data are displayed as number of patients. *$p < 0.05$, with or without fistulas in AP was related to CG.

Abbreviations: AP, apical periodontitis; CG, cheilitis granulomatosa.

4 | DISCUSSION

Cheilitis granulomatosa, also known as Miescher cheilitis, is a rare disease clinically characterized by recurrent or persistent swelling of one or both lips in the absence of systemic disease and histologically by non-necrotizing granulomas.[15] CG is also one of the manifestations of MRS and OFG. Generally, OFG contains CG and MRS.[16] In our study, we clinically reviewed patients with symptoms of CG and divided them into three subgroups – CG only, MRS, and OFG – to evaluate the association between granulomatous lip swelling and endodontic condition of teeth.

The etiology of CG has not been wholly elucidated, and multiple factors such as genetic, immunological, allergy, and infection have been postulated.[16] Microbiologic agents have been reported to be associated with chronic granulomatous diseases, including CD,[17] tuberculosis, and sarcoidosis.[18] CG is also histologically characterized by granulomatous infiltrate; thus, microbiologic agents may also play a suspected role in CG. To date, several cases have shown that dental infections may be the direct and initial etiology of CG,[5,10,19] and improvement of CG is reportedly observed after elimination of dental focal infection.[12,20] Furthermore, a recent study by our group showed that the microbiome composition of saliva samples from patients with CG was more diverse than those from healthy controls, and most of the genera observed in CG patients were associated with pulp infection.[21] Hence, it is of great value to investigate the association between dental infection and lips swelling in CG, MRS, and OFG. However, as CG is a rare disease, the association between dental infection and CG in large hospital cases with cohort controls has yet to be evaluated. This case–control study retrospectively analyzed CG cases (n = 181) and controls (n = 181) and showed that dental caries and AP were closely related ($p < 0.001$) to CG. The presence or absence of fistulas in AP lesions was also associated with occurrence of CG. It is possible that the fistulas of AP may contribute to the different microbiome composition of saliva samples between patients with CG and healthy controls.[21] Moreover, the location of AP foci (upper, lower, or both jaws) was highly associated with the location of lip swelling (upper, lower, or both lips), suggesting that patients with upper lip swelling have a potentially higher possibility of having periapical lesions in the maxillary region, while those with lower lip swelling have a potentially higher possibility of having periapical lesions in the mandibular area. Locational association indicates that adjacent infections of AP may be the main sources of infection in CG. However, not all odontogenic infections show a locational relationship with swelling lips. In our study, we did not find the locational relationship between dental caries and CG. We speculated that pathogens of dental caries may spread throughout the oral cavity through saliva, while etiologic agents of AP may be limited to the root canals;[21–23] hence, the foci of infected root canals may have more positional relation with the foci of lip swelling. The present study cannot explain the infective routes of CG; bacteria from infected root canals may elicit inflammatory cytokines

to stimulate adjacent soft tissues such as the lips. Besides, adjacent infections may spread to the lips by blood circulation as they are rich in vessels.[24,25]

Although there was an association between odontogenic infections and labial granulomatous swelling, we cannot explain the causative mechanisms. Previous studies have shown that bacterial antigen stimulation may result in abnormalities of macrophage function (secreting abnormal levels of inflammatory cytokines) in chronic granulomatous disease.[26,27] Apart from innate immunity, one group investigated clonal expansion of T cells and suggested that chronic antigen stimulation led to clonal expansion or increased secretion of cytokines by the lymphocyte clone-provoked granulomatous inflammation.[28] To sum up, combined with the results of this study, we speculate that chronic exposure to dental microbial antigens could possibly result in activation of immune response and thus trigger the granulomatous lesions in lips. Identification of bacteria, associated virulence factors, and cytokines within/around foci of dental infections and granulomatous lesions may further explain the relationship of these two diseases and improve the understanding of the pathogenesis of CG. Future studies may focus on the immunological mechanisms or various inflammatory/immunological mediators in dental infections and CG to investigate the role and possible mechanism of odontogenic infection in granulomatous disease.

Takeshita *et al*.[12] once reported a case of CG with periodontitis, and showed that after 2 months of periodontitis therapy, the lips returned to normal size without recurrence. The periodontal condition including the PLI and CI-S were also recorded and analyzed in cases and controls. The results showed no statistical difference of PLI and CI-S between the two groups (Table S1). However, records of community periodontal index in our CG patients were incomplete. Evidence for this relationship is still needed in the future.

Our study has some limitations. The major limitation is related to the retrospective nature of the reviewed cohorts, which limited access to clinical details. The existing data could not be verified and no more potentially valuable data is available. Another limitation is whether dental infection predated CG is unknown, which may have some impact on our speculation that dental infection may be associated with the etiology of CG. Besides, swelling of lips in CG patients may influence fundamental self-care behavior for maintenance of oral health such as toothbrushing and gargling; thus, the co-localization of the lower jaw infection in those with lower lip involvement and upper jaw infection in those with an upper lip involvement could be due to the difficulty in maintaining good oral hygiene. In the present study, there was no statistical difference of PLI and CI-S between cases and controls (Table S1), indicating that labial swelling might not affect the maintenance of oral hygiene. The results and conclusion of this study should be interpreted with caution, and further large-scale prospective studies should be carried out to validate our speculation.

Thus far, to our best knowledge, there is no definitive therapy for CG because the etiology is unknown. Traditionally, the first-line treatment is to prescribe corticosteroids both in the form of local injection and systemically.[29–31] However, long-term use of corticosteroids is associated with unpleasant side-effects.[32] The results of our study provide a new direction for management of swelling lips management in CG, MRS, and OFG patients. The present study reminds us that thorough examination for dental foci of infection should be performed before treating a patient with CG. Dental treatment may be a very effective and safe treatment of CG. In the future, long-term interventional studies to determinate the effect of dental treatment on CG should be conducted, not only with regard to improving the understanding of the etiology and infective sources of CG but also to provide a further therapeutic avenue for swollen lips in CG.

To the best of our knowledge, this is the first case–control study to report the association between dental infections and swelling lips in CG/MRS/OFG. On the basis of the results of this hospital-based, case–control study, there was an association between dental infections and granulomatous lip swelling, which may provide inspiration for future research of CG etiology and treatment. Well-designed longitudinal studies are needed to support any premise that treatment of dental infections could improve the swelling of CG patients. Moreover, further research may focus on exploring why dental infections are associated with labial granulomatous lesion and the underlying pathological mechanism.

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CONFLICT OF INTEREST

None declared.

ORCID

Yixiao Xing https://orcid.org/0000-0002-6283-1163
Hong Hua https://orcid.org/0000-0003-1198-508X

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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