Characterizing disease manifestations and treatment outcomes among patients with orofacial granulomatosis in China

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Background: Racial variation exists in the incidence of orofacial granulomatosis (OFG). The epidemiology and clinical characteristics of OFG in Asian countries are poorly described.

Objective: To describe the epidemiologic and clinical features of OFG in China from data collected on chronic odontogenic infection and studied in actual practice regarding the long-term outcome of OFG patients receiving different treatments.

Methods: Data on demographics, medical history, chronic odontogenic infection, and the extent of disease were collected, and long-term outcomes after the end of treatments were evaluated.

Results: Of the 165 OFG patients, 118 (71.5%; 95% CI 64.6%-78.5%) had a chronic odontogenic infection. There was a variety of difference between OFG with and without chronic odontogenic infection. Approximately 98.3% (95% confidence interval 94.8%-100%) of OFG patients with chronic odontogenic infection who received dental treatment showed a marked response, of whom 31 patients (53.4%; 95% confidence interval 40.2%-66.7%) had complete remission.

Limitations: Endoscopic investigations were not performed for most of the patients, and more detailed data were not collected, which might have demonstrated additional systemic problems.

Conclusions: OFG with chronic odontogenic infection is the major clinical pattern of OFG in China, which may be a subtype of OFG. Dental treatment should necessarily be the preferred first-line therapy for such patients. (JAAD Int 2020;1:126-34.)

Key words: dental treatment; granulomatous cheilitis; long-term outcome; odontogenic infection; orofacial granulomatosis; periapical infection.

Orofacial granulomatosis (OFG) is a chronic inflammatory disease characterized by nontender, recurrent, labial swelling of the maxillofacial region.[1] It may be idiopathic, which is localized only in the oral mucosa or in the skin and subcutaneous tissues of the oral cavity and face, such as granulomatous cheilitis. It may also be present in several systemic diseases, such as Melkersson-Rosenthal syndrome, Crohn's disease, sarcoidosis, and hypersensitivity reactions.[2,3] Most of these lesions present histopathologically as noncaseating granulomas, giving a nonspecific depiction and leading to a diagnostic impasse. The true prevalence of OFG is unknown; however, emerging evidence

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has shown the existence of racial differences in OFG.[4] In Europe, its increased prevalence has been suggested in the white population.[4] The literature available from Asian countries is limited.

The etiology of OFG is poorly understood, although several contributing factors have been proposed, including vasomotor disturbances,[5] hereditary factors,[5,6] infectious agents,[7] and allergens.[8] The multiple causes and clinical features have created confusion. Although the early literature identified several cases of OFG associated with dental infection,[4,9] the epidemiology of odontogenic infection in OFG patients is poorly described, without any emphasis on the diagnosis and treatment of dental infections. OFG patients are primarily given symptomatic treatment, with corticosteroids being the predominant medicine used either systemically or in the form of local injection.[10] Dental treatment has not been given priority in OFG treatment.

This study aimed to describe the demographic and clinical features of OFG in China. Data on odontogenic infection were collected, followed by the comparison of multiple variables among OFG patients without odontogenic infection and those with it. Moreover, particular emphasis was given to the long-term outcome of OFG patients with odontogenic infection who received dental treatment compared with intralesional corticosteroid therapy and thalidomide treatment.

CAPSULE SUMMARY

- Racial variation exists in the incidence of orofacial granulomatosis. The epidemiology and clinical characteristics of orofacial granulomatosis in Asian countries are poorly described.
- Orofacial granulomatosis with chronic odontogenic infection is the major clinical pattern of the disease in China. Dental treatment should necessarily be the preferred first-line therapy for such patients.

MATERIALS AND METHODS

Patients

Data were collected from the National Clinical Research Center for Oral Disease of China. All eligible patients who fulfilled the diagnostic criteria for OFG between 2012 and 2018 according to currently accepted criteria[11-13] were included in the study. Diagnostic criteria included the presence of clinical features belonging to the spectrum of OFG (Supplemental Table I) and representative incisional biopsy performed during initial consultations wherever possible the relevant histopathology was obtained. Hematologic tests were performed for some of the patients as they were required for diagnostic purposes, including complete blood cell count, general biochemistry, liver and adrenal function tests, autoantibodies, erythrocyte sedimentation rate, and QuantiFERON-TB. Patch testing and enteroscopy were performed to evaluate potential hypersensitive disease and gastrointestinal involvement.

The following data were obtained from the patient's medical records: age at disease onset, disease duration before treatment, sex, location of the orofacial sites involved, therapy given, recurrences, length of the observation period, extraoral manifestation, and medical history. Patients with dental caries or immobilization prostheses were further examined through radiographic imaging to determine chronic odontogenic infection. The records of only conspicuous cases of periapical infection were included.

Treatment

In this observational study, a total of 165 OFG patients were enrolled, and the patient flow chart is presented in Fig 1. In total, 128 OFG patients were eligible for the analysis of treatment efficacy. Among them, 59 patients received conventional intralesional corticosteroid injection, 58 patients with obvious chronic odontogenic infection received dental treatment, and the remaining 11 patients were treated with thalidomide.

The intralesional corticosteroid injections using compound betamethasone (5 mg betamethasone dipropionate/2 mg betamethasone sodium phosphate) were administered once a month in 3 courses. The dental treatment included root canal and the extraction of teeth with poor prognosis. Thalidomide in the thalidomide group was given at 50 mg daily for 1 month. A follow-up of over 6 months was performed to assess the efficacy of treatment. The treatment outcome was divided into 4 groups; namely, no response, initial response followed by relapse, partial remission, and complete remission. Both partial and complete remission without relapse were considered as remission maintenance of treatment. When disease recurred for more than 6 months after treatment completion, further therapy was given (data not shown).

Statistical analysis

The data obtained were recorded and processed with SAS (version 9.4, SAS Institute, Inc, Cary, NC). The results are expressed as median (range) and mean ± standard deviation where appropriate. Data

Abbreviations used:

CI: confidence interval
OFG: orofacial granulomatosis

were analyzed by Student *t* test, Mann-Whitney *U* test, χ^2 test, Kruskal-Wallis, analysis of variance, and binary and multinomial logistic regression analysis with Wald statistic, where applicable. Two-sided $P < .05$ was considered statistically significant.

RESULTS

Baseline characteristics of all OFG patients

During the study period, 165 OFG patients were enrolled from the Chinese Han population. Patients' baseline characteristics are reported in Table I. The median age at presentation was 49 years (range 5-83 years), with a median disease duration of 12 months (range 1-240 months). A total of 117 patients (70.9%; 95% confidence interval [CI] 63.9%-77.9%) were women, with peak incidence in the fifth and sixth decades (Fig 2). The mean age for men was 41.6 years (± 17.6 years; range 5-77 years); for women, 50.8 years (± 11.7 years; range 7-83 years). This difference was statistically significant ($P < .001$).

Approximately one-fifth of the patients (32/165; 19.4%; 95% CI 13.3%-25.5%) had a history of food or drug allergies, and 45 (27.3%; 95% CI 20.4%-34.1%) had a history of a cardiovascular disease. Of these, there were more hypertensive patients (38/45; 84.4%). A total of 15 patients (9.1%; 95% CI 4.7%-13.5%) had digestive system problems, including 3 with fatty liver, 5 with gallstones, 2 with cholecystitis, and 5 with gastritis. A total of 9 patients (5.5%; 95% CI 1.9%-8.9%) had granuloma-related diseases, including 6 with Melkersson-Rosenthal syndrome, 1 with cranial granuloma, 1 with sinus granuloma, and 1 with skin granuloma (not listed in Table I).

Seventy-three patients (44.2%) had lower lip swelling, 44 (26.7%) had upper lip swelling, and 48 (29.1%) had swelling in both lips. There were 57 patients (34.5%) with sole lip swelling, 30 (18.2%) had intraoral signs, and 78 (47.3%) had perioral or facial swelling and erythema.

Baseline characteristics according to odontogenic infection

A total of 118 of 165 patients (71.5%; 95% CI 64.6%-78.5%) had a chronic odontogenic infection, composing the majority of all OFG cases. Detailed data are shown in Table I. In the OFG patients with odontogenic infection, there was a significant female predominance (94/118; 79.7%; 95% CI 72.3%-87.0%) in contrast to that in the OFG patients without odontogenic infection (23/47; 48.9%; 95% CI 34.1%-63.8%) ($P < .001$). The mean age of onset of OFG for patients without odontogenic infection was 36.5 ± 17.9 years; for OFG patients with odontogenic infection, 50.5 ± 10.6 years. Although the patients had a history of a wide variety of medical problems, except hypertension, no significant difference was observed in the medical problems between the OFG patients without odontogenic infection and those with it.

The clinical manifestation of OFG at presentation is shown in Table I. Approximately one-third of the OFG patients without odontogenic infection (15/47; 31.9%) had upper lip involvement, one-third had lower-lip involvement (16/47; 34.0%), and one-third had both lips involved (16/47; 34.0%). In the OFG patients with odontogenic infection, the lower lip was affected in 48.3% (57/118); however, 24.6% (29/118) and 27.1% (32/118) had swelling of the upper lip and both lips, respectively. Regarding extension of swelling, OFG patients with odontogenic infection had a significantly higher rate of perioral region involvement (60.2% vs 14.9%) but lower rates of sole lip manifestation (20.3% vs 70.2%) compared with OFG patients without odontogenic infection ($P < .001$).

Follow-up data of 59 OFG patients receiving intralesional diprospan as first-line treatment

Overall, 59 OFG patients received intralesional corticosteroid injection, in which half of the patients were without odontogenic infections (30/59; 50.8%) and the other half were not (29/59; 49.2%) and were followed up for 38 (range 6-87) months. The characteristics of patients, according to their response, are shown in Table II.

The initial response was achieved in 50 of the 59 patients (84.8%; 95% CI 75.3%-94.2%), of whom 10 (16.9%; 95% CI 7.1%-26.8%) remained in remission for 19 months (range 6-64 months) after drug withdrawal, whereas there was a relapse in 40 patients (67.8%; 95% CI 55.5%-80.1%). The remaining 9 patients (15.2%; 95% CI 5.8%-24.7%) had no response. The response was not associated with age, sex, duration of disease, odontogenic infection, or disease severity.

Follow-up data of 92 OFG patients with odontogenic infection who received different treatments

The analysis included a total of 92 patients, who were followed up for 41 months (range 6-87 months) are shown in Table III. Initial response was achieved in 23 patients (79.3%; 95% CI 63.6%-94.9%) who received intralesional corticosteroid injection, in 57 (98.3%; 95% CI 94.8%-100%) who received dental treatment, and in 3 who received thalidomide.

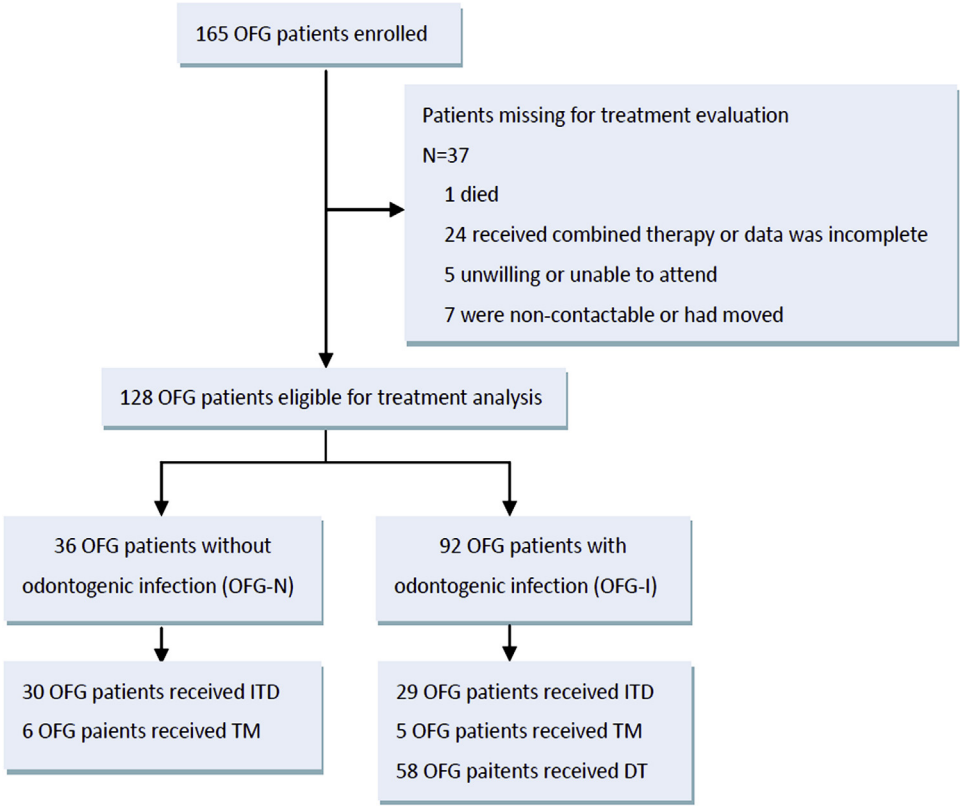

Fig 1. Flowchart of the orofacial granulomatosis patients being followed. One hundred twenty-eight patients were eligible for the treatment analysis (after exclusion, 1 died patient, 24 received combined therapy, 5 were unwilling or unable to attend, and 7 were noncontactable), 59 of 128 patients received intralesional corticosteroid injection, 11 of 128 patients who refused management with intralesional corticosteroid injection received thalidomide, and 58 of 128 with odontogenic infection consented to receive dental treatment as first-line treatment. *DT*, Dental treatment; *ITD*, intralesional compound betamethasone therapy; *OFG*, orofacial granulomatosis; *OFG-I*, orofacial granulomatosis infected; *OFG-N*, orofacial granulomatosis negative; *TM*, thalidomide therapy.

However, relapse occurred most frequently in the intralesional corticosteroid injection group (68.9%; 95% CI 51.1%-86.9%). In 3 patients, the progression of the disease was more severe after a brief remission. In contrast, no relapse occurred in the dental treatment group, and 57 of the 58 patients (98.3%; 95% CI 94.8%-100%) maintained remission after dental treatment for 41 months (range 6-83 months). Of these patients, 26 (44.8%; 95% CI 31.6%-58.0%) had partial remission, and 31 (53.4%; 95% CI 40.2%-66.7%) had complete remission. The relapse ratio in the thalidomide group was slightly lower (20%; 95% CI 0%-75.5%) than that in the intralesional corticosteroid injection group. After the multinomial logistic regression model analysis, dental treatment was identified as an independent predictor of remission maintenance ($P < .001$; risk ratio 90.1; 95% CI 15.4-527.9).

DISCUSSION

Microbial factor plays a significant role in the pathogenesis of several granulomatous diseases.[14,15] However, to date, the epidemiologic literature on local chronic infection in OFG presentation is scarce. To investigate the effects of local infection on OFG, we conducted a pilot study to consider chronic odontogenic infection and compared multiple variables among OFG patients without odontogenic infection and those with it. Although the odontogenic infection criteria used were strict, we found that 71.5% of patients (95% CI 64.6%-78.5%) had apical periodontitis, composing the majority of all OFG cases and more than 5 affected teeth in a few cases. The apical periodontitis in OFG patients with odontogenic infection is usually asymptomatic, without complaint of sharp, severe pain, which is the most common presentation in patients with

Table I. Baseline characteristics and medical history for orofacial granulomatosis patients according to odontogenic infection

Variable	Total (n = 165)	OFG-N (n = 47)	OFG-I (n = 118)	*P* value
Age at disease onset, y	49 (5-83)	39 (5-72)	51 (20-83)	<.001
Age, y	51 (5-83)*	41 (5-72)*	53 (23-83)	<.001
Women	52 (7-83)	49 (7-72)	53 (23-83)	
Men	45 (5-77)	30 (5-63)	53 (32-77)	
Women, No. (%)	117 (70.9)	23 (48.9)	94 (79.7)	<.001
Duration of disease, mo	12 (1-240)	10 (2-120)	12 (1-240)	.32
Medical history, No. (%)				
Allergy	32 (19.4)	9 (19.1)	23 (19.5)	>.99
Cardiovascular diseases	45 (27.3)	8 (17.0)	37 (31.4)	.04
Digestive system diseases	15 (9.1)	4 (8.5)	11 (9.3)	>.99
Skin diseases	4 (2.4)	1 (2.1)	3 (2.5)	>.99
Endocrine diseases	3 (1.8)	1 (2.1)	2 (1.7)	>.99
Urinary system diseases	3 (1.8)	0	3 (2.5)	
Nervous system disease	3 (1.8)	0	3 (2.5)	
Respiratory disease	2 (1.2)	1 (2.1)	1 (0.8)	.49
Autoimmune diseases	2 (1.2)	1 (2.1)	1 (0.8)	.49
Genital system diseases	2 (1.2)	0	2 (1.7)	
Clinical characteristics of OFG				
Lip enlargement, No. (%)				.25
Upper lip	44 (26.7)	15 (31.9)	29 (24.6)	
Lower lip	73 (44.2)	16 (34.0)	57 (48.3)	
Both lips	48 (29.1)	16 (34.0)	32 (27.1)	
Extent of disease, No. (%)				
Solely lip manifestation	57 (34.5)	33 (70.2)	24 (20.3)	<.001
Intraoral manifestation	30 (18.2)	7 (14.9)	23 (19.5)	.66
Perioral or facial swelling, erythema	78 (47.3)	7 (14.9)	71 (60.2)	<.001

Data are expressed as median (range) unless otherwise indicated.
OFG, Orofacial granulomatosis; *OFG-I*, orofacial granulomatosis infected; *OFG-N*, orofacial granulomatosis negative.
*Indicates which group has been compared between women and men and that the difference is statistically significant.

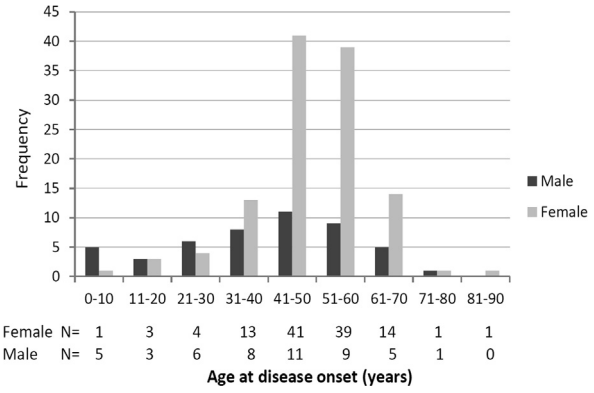

Fig 2. Age distribution at disease onset between the 165 male and female orofacial granulomatosis patients. The peak incidence was in the fifth and sixth decades.

apical periodontitis. This may be the primary reason that dental problems were not the chief presenting complaints of the patients, or were ignored by some dermatologists and even dentists. This situation was also reflected in some case reports.[16,17]

A number of studies have examined the role of sex bias in the incidence of OFG. Studies from Europe and North America found no significant difference.[18-22] In contrast, unlike earlier studies, we found that in China there was a higher prevalence of OFG in women (70.9%; 95% CI 63.9%-77.9%) than men, with the onset of symptoms usually occurring much later in life (50 years) than generally believed.[18-21] However, the sex bias disappeared once the OFG patients with odontogenic infection were not taken into account. We found that, based on data from OFG patients without odontogenic infection, the sex distribution was 23:24, with a female:male ratio of 1:1, which is similar to the levels that have been reported from Europe and North America.[18-22] Accordingly, we assumed that OFG patients with odontogenic infection and those without it might constitute 2 subtypes of OFG.

Based on this assumption, the data suggested that there was a vast difference between the subtypes. In

Table II. Demographic and clinical characteristics of compound betamethasone–treated patients according to response to treatment

Variable	No response (n = 9)	Relapse (n = 40)	Remission (n = 10)	*P* value
Age, y	45 ± 21	45 ± 15	47 ± 11	.93
Women, No. (%)	6 (66.7)	21 (52.5)	7 (70.0)	.53
Duration of disease, mo	22 ± 17	19 ± 23	25 ± 35	.78
Total follow-up, mo	30 ± 25	40 ± 28	28 ± 22	.35
Odontogenic infection, No. (%)	6 (66.7)	20 (50.0)	3 (30.0)	.30
Lip enlargement, No. (%)				.65
Upper	2 (22.2)	11 (27.5)	3 (30.0)	
Lower	5 (55.6)	12 (30.0)	4 (40.0)	
Both	2 (22.2)	17 (42.5)	3 (30.0)	
Extent of disease, No. (%)				.39
Solely lip manifestation	3 (33.3)	17 (42.5)	6 (60.0)	
Intraoral manifestation	5 (55.6)	16 (40.0)	2 (20.0)	
Perioral or facial swelling, erythema	1 (11.1)	7 (17.5)	2 (20.0)	

Data are expressed as mean ± standard deviation. Remission group included partial remission and complete remission cases.

the OFG patients with odontogenic infection, the sex distribution was 94 women to 24 men (women 79.7%; 95% CI 72.3%-87.0%), with a female:male ratio of 4:1, in contrast to that in OFG patients without odontogenic infection (women 48.9%; 95% CI 34.1%-63.8%; $P < .001$). There was a trend toward an earlier age of onset among the OFG patients without odontogenic infection, but a late onset among those with it (39 years [range 5-72 years] vs 51 years [range 20-83 years]; $P < .001$).

Moreover, all OFG patients had a clinical presentation of lip swelling, but those with odontogenic infection were more likely to show perioral erythema (60.2% vs 14.9%; $P < .001$). The proportion of OFG patients presenting with only lip manifestation was higher for those without odontogenic infection (70.2% vs 20.3%; $P < .001$). Intraoral signs, including cobblestone formation of the oral mucosa, mucosal tags, and gingival enlargement, were observed in 19.5% of OFG patients with odontogenic infection and 14.9% of those without it, without significant difference. In follow-up, only 2 OFG patients who subsequently developed Crohn's disease were without odontogenic infections. The difference in the incidence of hypertension between OFG patients without odontogenic infection and those with it may be attributable to the older age of the latter.

The incidence of OFG has increased during the last 50 years,[21,23] but there are no reliable epidemiologic data available. As a result, there is a very wide geographic and racial variation in the incidence of OFG.[24-26] A similar variation also exists in Crohn's disease, which is closely correlated with OFG. Crohn's disease is a chronic, granulomatous, inflammatory disease of the gastrointestinal tract that can affect any location in the tract, from the mouth to the anus.[27] OFG is one of the extraintestinal manifestations.[28-30] A previous study showed that the prevalence of Crohn's disease in whites was much higher than that in Asians.[31] Moreover, extraintestinal manifestations were observed to be more prevalent in whites compared with Asians,[32] which was further highlighted in a genotype-phenotype analysis.[33,34] There is limited literature on the epidemiologic distribution of OFG in Asian countries, but review of isolated case reports gives an impression that OFG with odontogenic infection is more prevalent in Asian countries, and a series of OFG patients with odontogenic infection cases has been amassed for Chinese and Japanese populations.[16,35-37] In the present study, all OFG patients were from the Chinese Han population, who had more incidence of the OFG concomitant with odontogenic infection, raising the possibility that there is a difference in incidence and clinical manifestations of OFG between the Western and Asian population.

Although this study primarily focused on orofacial presentation, a low proportion of patients also presented with other granuloma-related focuses, including cranial, sinus, and skin granulomas, implying that besides the orofacial region and gastrointestinal tract, other parts of the body might be involved.

The treatment of OFG remains controversial and challenging,[7,35,38] and several medications and therapies have been documented, including corticosteroids, chloroquine, sulfa drugs, tetracycline, antihistamines, isoniazid, repeated irradiation, and adalimumab.[39-43] Corticosteroid is the first-line treatment in OFG, which is used either systemically or injected locally.[10] Although a degree of success has been noted, corticosteroids are often used

Table III. Demographic and clinical characteristics and treatment outcome of the orofacial granulomatosis patients with odontogenic infection and receiving different treatments

Variable	Compound betamethasone (n = 29)	Dental treatment (n = 58)	Thalidomide (n = 5)	*P* value
Age, y	53 ± 9	51 ± 11	60 ± 6	.1
Women, No. (%)	22 (75.9)	46 (79.3)	4 (80.0)	.9
Duration of disease, mo	18 ± 22	26 ± 43	41 ± 33	.4
Total follow-up, mo	39 ± 29	35 ± 21	29 ± 28	.6
Lip enlargement, No. (%)				.9
Upper	8 (27.6)	15 (25.9)	1 (20.0)	
Lower	13 (44.8)	29 (50.0)	2 (40.0)	
Both	8 (27.6)	14 (24.1)	2 (40.0)	
Extent of disease, No. (%)				.8
Solely lip manifestation	5 (17.2)	13 (22.4)	2 (40.0)	
Intraoral manifestation	18 (62.1)	29 (50.0)	2 (40.0)	
Perioral or facial swelling, erythema	6 (20.7)	16 (27.6)	1 (20.0)	
Response to treatment				<.001
No response	6 (20.7)	1 (1.7)	2 (40.0)	
Relapse	20 (69.0)	0	1 (20.0)	
Partial remission	2 (6.9)	26 (44.8)	2 (40.0)	
Complete remission	1 (3.4)	31 (53.4)	0	

Data are expressed as mean ± standard deviation.

temporarily or in conjunction with other medications. Recurrence or even aggravation of OFG in some patients treated with corticosteroid[17] highlights the need for further high-quality, adequately powered trials.

The current study assessed intralesional compound betamethasone therapy in OFG patients, and special emphasis was given to the long-term outcome of patients. Initial response can be achieved in most cases (84.8%; 95% CI 75.3%-94.2%). However, relapse was noted in 40 patients (67.8%; 95% CI 55.5%-80.1%) after betamethasone withdrawal. The analysis in the OFG patients with odontogenic infection who received different treatments showed that relapse occurred in 68.9% (95% CI 51.1%-86.9%) of those who received intralesional corticosteroid injection, and in 3 patients there was a more severe progression of the disease after a brief remission, which might be related with the negative effect of corticosteroids on the infection.

Corticosteroid, an anti-inflammatory medication, is a risk factor for infection remission.[44,45] A survey carried out in a population aged 50 years and older showed that corticosteroid use was directly associated with the extent and severity of odontogenic infections.[46] In 2013, Jentsch et al[47] investigated the effect of corticosteroid on periodontitis-related bacteria and showed that the growth of a few bacteria was increased by cortisol, which provided a certain proof for the negative effect of corticosteroids on odontogenic infection. On the contrary, approximately 98.3% of the patients (95% CI 94.8%-100%) showed a marked response to dental treatment, as verified in earlier cases,[16,36] which suggested the role of dental treatment as the first-line therapy in OFG patients with odontogenic infection.

However, not all OFG patients with odontogenic infection were cured after receiving dental treatment. There were 26 patients (44.8%; 95% CI 31.6%-58.0%) who had partial remission without relapse, which suggested that odontogenic infection was not the only cause for OFG. Other treatment methods may still be required after the infection is removed, including corticosteroid.

In conclusion, to our knowledge our study is the first to show that OFG patients without odontogenic infection and those with it represent 2 subtypes of OFG, and OFG patients with odontogenic infection compose the majority of cases in China. For OFG patients with odontogenic infection, dental treatment should be considered as first-line therapy.

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Supplementary Table I. The spectrum of OFG

Intra-oral manifestations
Cobblestoning
Gingival enlargement
Mucosal tags
Fissured tongue
Extra-oral manifestations
Lip swelling
Perioral swelling or erythema
Facial swelling
Angular cheilitis