Dermatology

Review Article

Dermatology 2021;237:635–640
DOI: 10.1159/000513446

Received: June 25, 2020
Accepted: November 29, 2020
Published online: February 12, 2021

Orofacial Granulomatosis and Crohn Disease: Coincidence or Pattern? A Systematic Review

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Keywords
Orofacial granulomatosis · Tongue, fissured · Facial paralysis · Granulomatosis, orofacial · Crohn disease

Abstract
Background: To systematically review all cases of orofacial granulomatosis (OFG) and evaluate the association between OFG and Crohn disease (CD). ***Summary:*** This review was conducted according to PRISMA guidelines and a search of the PubMed, MEDLINE, and Embase databases, and the Cochrane Library in March 2020, using keywords and MeSH terms associated with "orofacial granulomatosis," "Crohn disease," and their variants, with no language restrictions and across all age groups. All relevant articles were accessed in full text. Single case reports and articles on sarcoidosis, allergy, ulcerative colitis, and infectious diseases were excluded from the analysis. ***Results:*** We retrieved 507 reports on OFG. The mean age at onset was 23.3 years (range 2–89 years). A total of 240 (47.3%) females and 267 (52.6%) males were included. CD was present in 93 children aged <16 years (68.3%) and in 43 adults (31.9%). In most cases, the OFG appeared before the CD. The most common clinical manifestations were intraoral mucosa abnormalities (n = 251; 49.5%), lower-lip swelling (n = 249; 49.1%), upper-lip swelling (n = 227; 44.7%), and gingivae (n = 193; 38.7%). Patients with concurrent CD were more likely to experience involvement of the buccal sulcus. ***Key Messages:*** OFG presents primarily as a solo entity. The OFG that was associated with CD was present in 93 children aged under 16 years (68.3%) and in 43 adults (31.9%). Childhood onset of OFG carries with it a higher risk of developing CD.

Introduction

Orofacial granulomatosis (OFG) is a term that encompasses persistent orofacial swelling and histological evidence of noncaseating granulomas [1]. Its prevalence is unknown. OFG may occur at any age but appears most frequently in young adults. No predilection according to race or sex has been consistently demonstrated. Clinically, it can affect all facial tissues, with the lips being the most common site of recurrent, painless, and nonpruritic edema (Fig. 1, 2). Additional features include oral

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ulceration, gingival involvement, angular cheilitis, and vertical fissures of the lips [1]. The pathogenesis of OFG is largely unknown but it has been attributed to several causes, including food allergies, microbial agents, dental material, immunological hypersensitivity, and genetics [1].

Several groups consider OFG an umbrella term that encompasses other diseases that concur with persistent orofacial swelling and granulomatous inflammation, such as Crohn disease (CD) and Melkersson-Rosenthal syndrome (MRS) (defined by the triad of orofacial swelling, facial palsy, and plicated tongue). The exact relationship between CD and OFG remains unknown, but it has been suggested that these entities are part of the same clinical-pathological spectrum. Several similarities between OFG and CD favor this theory: indistinguishable granulomatous histopathological exams between the diseases, recurrent course, similar treatments, and oral manifestations (such as lip and oral mucosa edema, gingival overgrowth, gingival fistulae, and palate lesions) [2–6].

The association between OFG and CD ranges from 8 to 46% of OFG cases, and some groups have failed to demonstrate a link between the diseases [2, 4, 7–9]. Studies on exclusively pediatric age groups have reported a 40% association between OFG and CD, suggesting that the onset of OFG in childhood is a predictive factor for the development of CD [10].

Here, we review pediatric and adult cases of OFG and identify the relationship between OFG and/or MRS and CD.

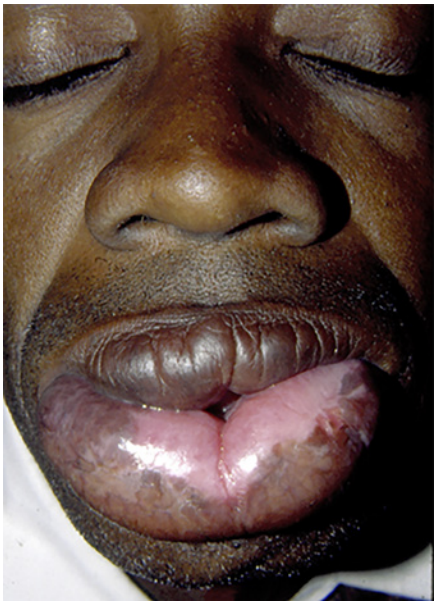

Fig. 1. Exuberant enlargement of the upper and lower lip.

Methods

This review was performed according to PRISMA guidelines [11], and the search was completed using the PubMed, MEDLINE, and Embase databases, and the Cochrane Library in March 2020. The search strategy comprised keywords and MeSH terms associated with "orofacial granulomatosis," "Crohn disease," and their variants, with no language restrictions. The relevant articles were accessed in full text.

Our inclusion criteria were primary studies in humans that reported an association between OFG and/or MRS and CD. Single case reports, reviews, and articles on sarcoidosis, allergy, ulcerative colitis, and infectious diseases were excluded from the analysis.

An adjusted form of the Joanna Briggs Critical Appraisal Tool for prevalence studies was used to assess the quality of the studies, and data on patients and disease characteristics were extracted, analyzed, and summarized.

The database search yielded 341 results, as shown in the PRISMA flow diagram (Fig. 3). Two of the authors (C.F.B.G. and G.P.F.) independently screened and reviewed the titles and abstracts that were identified in the electronic databases to establish eligibility. For records deemed to be relevant, the full-text studies were then reviewed independently by these 2 authors according to the inclusion and exclusion criteria. A third author (M.L.D.D.) independently resolved any disagreements. After the inclusion of all relevant studies, data extraction was performed.

Ultimately, 14 studies satisfied the inclusion criteria, had data extracted, and were included in the analysis. All included records were case series studies. The data from these studies are summarized in Table 1.

Results

This study comprised data on 507 patients, 240 (47.34%) females and 267 (52.66%) males, with a mean age of 23.34 ± 14.91 years (range 2–89 years). Examination of gastrointestinal alterations by colonoscopy was reported in 342 patients (67.46%).

A total of 353 (69.63%) patients were reported to have OFG without any other systemic disease. The other 154 patients (30.37%) were diagnosed as having both OFG and CD; 107 (21.10%) described gastrointestinal clinical symptoms, and there was detailed information on 50 cases (Table 2). Two of the included studies did not report the number of pediatric patients aged <16 years with OFG or presented only the average age and range for those with OFG and those with OFG and CD but did not record the age of each patient. The remaining 12 studies described

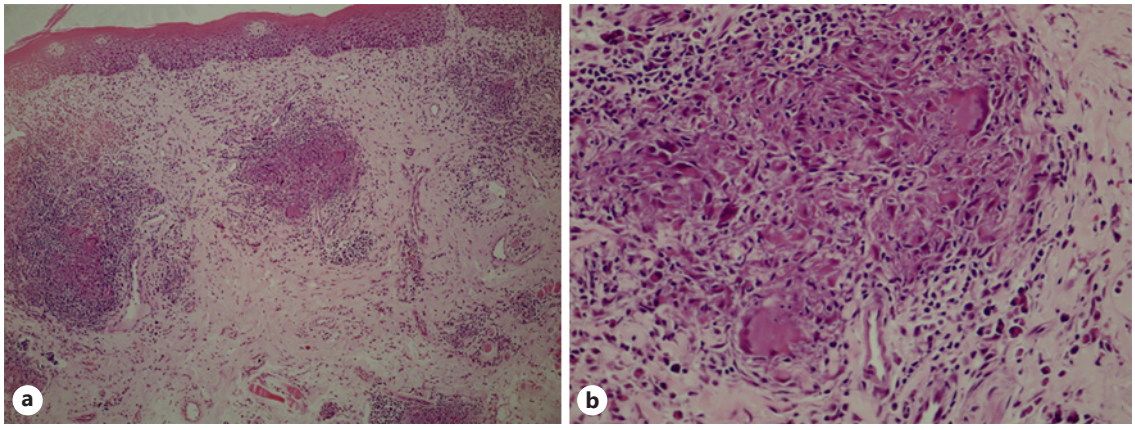

Fig. 2. a Well-formed granuloma in OFG, intermingled with intense edema in the superficial lamina propria and surrounded by lymphoplasmacytic inflammatory infiltrate. HE. ×40. **b** Well-formed granuloma with epithelioid and multinucleated giant cells. HE. ×400.

the age variance between groups, and of the 283 patients with a diagnosis of OFG, 107 (37.8%) were <16 years and 176 (62.1%) were adults. OFG that was associated with CD was present in 93 children aged <16 years (68.3%) and in 43 adults (31.9%) (Table 3). The most frequently reported association of OFG with CD was noted in the pediatric age groups.

Not all reports detailed the chronological onset of orofacial and intestinal symptoms. In 49 cases (9.66%), the OFG appeared before the CD (a mean time from OFG diagnosis to CD diagnosis of 2.37 years). In 33 cases, CD appeared before the diagnosis of OFG (a mean time from CD diagnosis to OFG diagnosis of 5.9 years). In 23 cases, the diagnosis was simultaneous. A family history of CD was reported in 10 patients (6.2%).

The most common clinical manifestations were intraoral mucosa abnormalities (n = 251; 49.51%), lower-lip enlargement/swelling (n = 249; 9.11%), upper-lip compromise (n = 227; 44.7%), and gingival alterations (n = 193; 8.7%) (Table 4). Fourteen patients (2.76%) had features that were consistent with classic MRS, with a complete clinical presentation of the typical triad of symptoms, i.e., facial edema, fissured tongue, and facial palsy.

In general, there were no significant differences in the clinical manifestation of OFG with or without CD, except with regard to the involvement of the buccal sulcus, i.e., 1 study demonstrated that patients with concurrent CD were more likely to experience involvement of the buccal sulcus (with erythema, ulceration, and granuloma) [3].

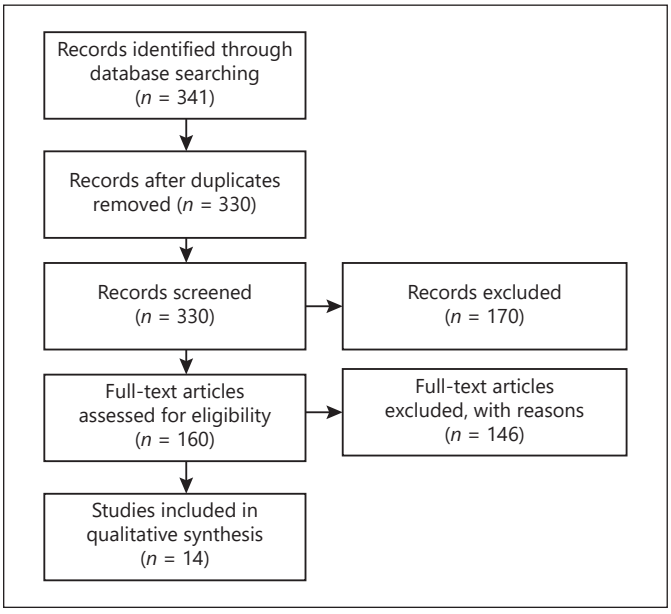

Fig. 3. Flow diagram of the selection of the studies.

Discussion

OFG is a rare disease with an unknown cause and an estimated incidence of 80/100,000 per year [12]. This review highlights reports on the association of OFG and CD. CD was diagnosed in 30.3% of patients with OFG. This association was more likely to occur when the onset of OFG was in childhood, and especially when associated with a manifestation of perianal disease. In most cases,

Table 1. Origin, sample size, and frequency of OFG and CD manifestations

First author [ref.], year	Country	Total (n = 507)	OFG, n (%)	CD + OFG n (%)
Haaramo [15], 2017	Finland	29	9 (27.6)	21 (72.4)
Mutalib [16], 2016	England	29	10 (34.5)	19 (65.5)
Ratzinger [17], 2007	Austria	14	10 (71.4)	4 (28.5)
Tuxen [18], 2010	Australia	7	2 (28.6)	5 (71.4)
Campbell [3], 2011	UK	207	161 (77.8)	46 (22.2)
Wiesenfeld [2], 1985	UK	60	54 (90)	6 (10)
Lazzerini [19], 2015	Italy	5	0 (0)	5 (100)
Sciubba [7], 2003	USA	13	7 (53.8)	6 (46.1)
Saalman [20], 2009	Sweden	8	4 (50)	4 (50)
van der Waal [21], 2002	The Netherlands	13	11 (84.6)	2 (15.3)
Marcoval [22], 2016	Spain	22	22 (100)	0 (0)
Gale [14], 2015	Sweden	29	17 (58.6)	12 (41.3)
Sanderson [13], 2005	UK	35	16 (45.7)	19 (54.2)
Gavioli [23], 2020	Brazil	36	31 (86.1)	5 (13.8)

Table 2. Gastrointestinal clinical symptoms in 50 patients diagnosed with Crohn's disease (extracted from the reports with a detailed description of clinical signs and symptoms)

Clinical features	n (%)
Perianal disease	29 (50.5)
Diarrhea	18 (36)
Constipation	12 (24)
Abdominal pain	9 (18)
Flatulence	6 (12)
Bloody stools	2 (4)

CD was confirmed in the first years (a mean of 2.37 years) after OFG was diagnosed.

There were no significant differences in the clinical manifestations of OFG with or without CD, but concurrent CD should be suspected in patients with elevated inflammatory markers, an abnormal complete blood count as well as a clinical presentation of greater sulcal involvement, oral ulceration, and less lip involvement [3]. CD should also be suspected in children with OFG, as was shown by the additional discrimination between pediatric and adult patients, with a higher association of OFG with CD revealed in children. This pattern was also observed in a systematic review by Lazzerini et al. [10], who noted a higher correlation of CD in patients with an earlier onset of OFG. A longer and detailed intestinal follow-up of patients who manifest oral symptoms in childhood for the development of CD is recommended [13].

The rate of association between OFG and CD in this review may have been underestimated, because CD was not systematically assessed in patients without intestinal symptoms, the follow-up duration was short in most of the reports, some treatment modalities for OFG might have silenced the intestinal disease, and publication bias could have affected the characteristics of the reported cases.

The remaining cases of OFG without confirmation of CD might refer to MRS. The diagnosis of MRS is often difficult because the classic triad of symptoms is not always present. Obtaining a diagnosis of MRS is, in general, lengthy, as it is based on the disease course and clinical features. The histopathological criteria might not be characteristic of the disease, as the microscopic presentation can vary from edema and congestion to lymphoplasmacytic inflammatory infiltrate and granulomas, depending on the disease stage. Thus, in the absence of granulomas, a diagnosis of MRS should not be excluded.

CD can affect the entire gastrointestinal tract, including the oral cavity structures (oral CD). With their clinical and histopathological overlap, the relationship between OFG and CD is debatable, but emerging evidence suggests that they are distinct diseases [3, 13, 14]. Sanderson et al. [13] evaluated 35 patients with OFG and no gastrointestinal symptoms, who underwent ileocolonoscopy and intestinal biopsy. Macroscopic abnormalities in the intestine, such as aphthoid ulcerations and extensive ulcers, were detected in 54% of cases, and granulomas were present in 64%. Most of the patients remained free of in-

Table 3. Age discrimination of OFG and CD onset in 507 patients

First author [ref.], year	OFG			OFG + CD			Total
	children (<16 years)	adults	*n* (%)	children (<16 years)	adults	n (%)	
Haaramo [15], 2017	8	0	8 (27.6)	21	0	21 (72.4)	29
Mutalib [16], 2016	10	0	10 (34.5)	19	0	19 (65.5)	29
Ratzinger [17], 2007	0	10	10 (71.4)	1	3	4 (28.5)	14
Tuxen [18], 2010	2	0	2 (28.6)	5	0	5 (71.4)	7
Campbell [3], 2011	68	93	161 (77.8)	16	30	46 (22.2)	207
Wiesenfeld [2], 1985	n.i.	n.i.	54 (90)	4	2	6 (10)	60
Lazzerini [19], 2015	0	0	0 (0)	5	0	5 (100)	5
Sciubba [7], 2003	0	7	7 (53.8)	7	0	6 (46.1)	13
Saalman [20], 2009	4	0	4 (50)	4	0	4 (50)	8
van der Waal [21], 2002	0	11	11 (84.6)	0	2	2 (15.3)	13
Marcoval [22], 2016	0	22	22 (100)	0	0	0 (0)	22
Gale [14], 2015	12	5	17 (58.6)	10	2	12 (41.3)	29
Sanderson [13], 2005	n.i.	n.i.	16 (45.7)	n.i.	n.i.	19 (54.2)	35
Gavioli [23], 2020	3	28	31 (86.1)	1	4	5 (13.8)	36

OFG, orofacial granulomatosis; CD, Crohn disease; n.i., not indicated.

Table 4. Orofacial manifestations in 507 patients diagnosed with orofacial granulomatosis

Clinical features	*n* (%)
Lip swelling	
Upper lip	227 (48.2)
Lower lip	249 (52.8)
Unspecified	26 (5.5)
Facial swelling	
Cheeks	29 (5.72)
Forehead	2 (0.39)
Eyelids	2 (0.39)
Nose	2 (0.39)
Intraoral manifestations	
Gingivae	193 (38.07)
Hard palate	19 (3.75)
Soft palate	5 (0.9)
Tongue	35 (6.9)
Oral mucosa	251 (49.51)
Buccal sulcus	36 (7.1)
MRS triad	14 (76)

testinal symptoms during several years of follow-up, prompting the group to conclude there are 3 distinct entities: classic oral CD (when the patient presents with a diagnosis of established gastrointestinal CD with oral involvement), OFG with gastrointestinal involvement (patients have OFG with subclinical or asymptomatic endoscopic alterations), and OFG without intestinal involvement [13]. According to this review, it is clear that most patients who present with OFG do not have CD or fail to develop the condition.

The key to distinguishing these conditions lies in unraveling their genetic basis, but few studies on this are available. Gavioli et al. [23] demonstrated that HLA-specific alleles could be hallmarks of patients with MRS and other studies implicated differences in nucleotide oligomerization domain 2 (*NOD2*) as being strongly associated with CD. These genetic bases support the acceptance that OFG and CD are distinct entities but that they can be linked in certain cases.

Publication bias, risk of bias assessment, inconsistent or poorly reported study methods, and nonstandardized outcomes limit the conclusions that can be made in this review.

Conclusion

This review examined the relationship between OFG and CD. The use of OFG as an umbrella term should be avoided, and efforts to classify OFG cases into specific diagnoses would improve treatment and follow-up. Approximately 30.3% of cases presented with OFG with concurrent CD. Sulcal involvement, ulceration, and elevated inflammatory markers should raise clinical suspi-

cion of CD. Childhood onset of OFG is a reason to suspect CD and a possible early manifestation of this disease. All patients who present with OFG should be examined for CD, regardless of symptomatology.

Key Message

We found that CD was present in 30.3% of OFG cases.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors received financial support from the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) (2017/26990–8, 2018/419–5).

Author Contributions

C.F.B.G. and G.P.F.: conception and design, acquisition of data, analysis and interpretation of data, drafting and revision of the manuscript, final approval of the version to be published. M.L.D.D. and M.R.J.: acquisition of data, analysis and interpretation of data. M.M.S.N.: drafting and revision of the manuscript, final approval of the version to be published. S.V.L.: conception and design, drafting and revision of the manuscript, final approval of the version to be published.

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