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ORIGINAL ARTICLE

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Orofacial granulomatosis: Clinical and therapeutic features in an Italian cohort and review of the literature

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Abstract

Background: Orofacial granulomatosis (OFG) is characterized by granulomatous inflammation of the soft tissues of maxillofacial region. We explored OFG patients from 10 different Italian centers and summarized the most recent literature data.

Methods: A review of patients with OFG was carried out. An extensive online literature search was performed to identify studies reporting diagnosis and management of OFG.

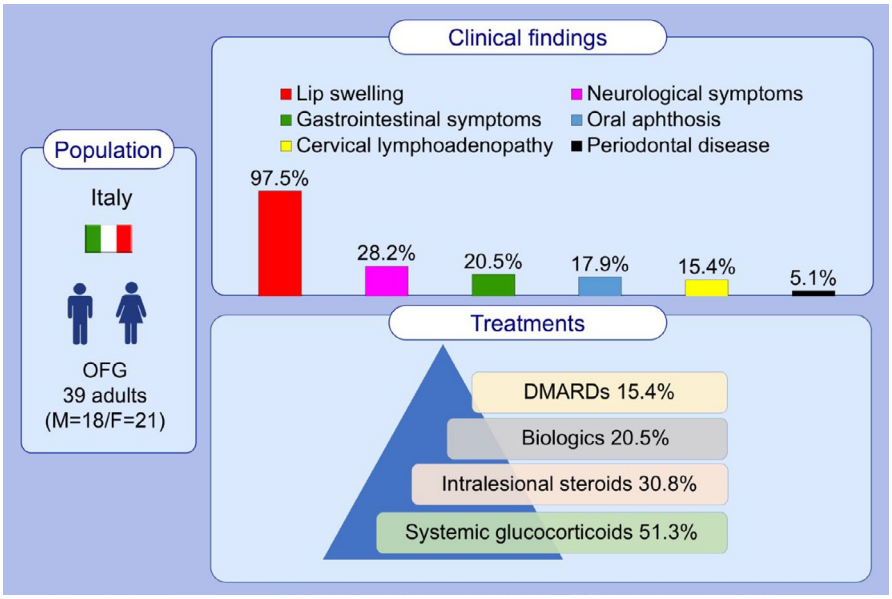
Results: Thirty-nine patients were recruited between January 2018 and February 2020. Most of them (97.4%) displayed involvement of the lips, and 28.2% suffered from Melkersson-Rosenthal syndrome. Two patients received diagnosis of CD and

Abbreviations: CD, Crohn's disease; GCM, granulomatous cheilitis of Miescher; GCs, glucocorticoids; H1, histamine receptor 1; IBD, inflammatory bowel disease; IgE, immunoglobulin E; IgG, immunoglobulin G; IgM, immunoglobulin M; IL, interleukin; MRS, Melkersson-Rosenthal syndrome; NSAID, non-steroidal anti-inflammatory drug; OFG, orofacial granulomatosis; SPT, skin prick test; TNF-α, tumor necrosis factor-α.

one patient of sarcoidosis, suggesting secondary OFG. Oral aphthosis and cervical lymphadenopathy were also described. The mean diagnostic delay was 3.4 years. Histological evaluation was performed in 34/39 patients (87.2%); non-caseating granulomas were found in 73.5% of them. Neurological symptoms (28.2%), gastrointestinal symptoms in absence of overt inflammatory bowel disease (IBD) (20.5%), and atopy (35.9%) were also identified. Therapeutic approaches varied among the centers. Steroids (51.3%) were used with good or partial results. Anti-TNF-α and anti-IgE monoclonal antibodies were used in 6 (15.4%) and 1 (2.6%) patients, respectively, with variable results. Surgery was the choice for 2 patients with good response.

Conclusions: OFG is a rare and neglected disease showing multiple clinical phenotypes. While early diagnosis is crucial, management is difficult and highly dependent on the expertise of clinicians due to the lack of international guidelines. There is a need to establish registry databases and address challenges of long-term management.

KEYWORDS
granulomatous cheilitis, Italian registries, Melkersson-Rosenthal syndrome, orofacial granulomatosis



GRAPHICAL ABSTRACT
This article provides a description of clinical features of 39 patients with OFG, a granulomatous inflammatory disease of soft tissues of maxillofacial regions. In the majority of patients, lip swelling is the first clinical manifestation of disease. Intralesional corticosteroids are a cornerstone of treatment and show the highest response rate in these patients. Abbreviations: DMARDs, disease-modifying anti-rheumatic drugs; OFG, orofacial granulomatosis
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1 | BACKGROUND

Orofacial granulomatosis (OFG) is a rare disorder characterized by persistent and/or recurrent labial enlargement and chronic non-caseous granulomatosis involving the soft tissue of the oral and maxillofacial regions.[1] This term includes the variants Melkersson-Rosenthal syndrome (MRS) and granulomatous cheilitis of Miescher (GCM).[2]

OFG, MRS, and GCM have been heterogeneously described throughout the years by the scientific literature. In many cases, their clinical characteristics overlap and it is unclear how to distinguish

the three different variants. In this article, we use the term GCM when the swelling involves just one or both lips and MRS when OFG is associated with cranial nerve involvement.

The exact prevalence of OFG is unknown, but it is considered a rare disease. The increased incidence of the last few years is likely due to the improved knowledge, but the condition still remains a neglected entity.[3] Secondary OFG can occur in the context of a systemic granulomatous disease such as Crohn's disease (CD) or sarcoidosis. In the absence of other systemic pathologies, OFG is defined as idiopathic. OFG was proposed as a variant of CD with the distinct feature as localizing to the oral cavity. Indeed, a considerable percentage of patients with OFG (about 40% in pediatrics and 20%–50% in adults) is diagnosed as CD.[4] These data could be underestimated, since intestinal involvement can be asymptomatic at the beginning.[5] Moreover, OFG can precede by many years the onset of intestinal symptoms and therapy can also partially mask the intestinal involvement.[6,7] Further studies, involving a larger number of patients, are required to clarify whether CD and OFG represent two distinct clinical entities or not. In the clinical practice, CD should be suspected in all patients with OFG and patients suffering from gastrointestinal symptoms need to undergo second-level investigations.[8] Oral ulcers, increased inflammatory markers, changes in blood counts, and pediatric onset of OFG are the main risk factors for progression to CD.[4]

International guidelines on diagnosis and therapy are missing, thus making the management of the disease often dependent on the single-center experience or based on expert opinion.

The objective of the present study was to describe the clinical presentation, treatment, and outcome of patients with OFG from 10 Italian centers and summarize the available literature regarding the diagnosis and treatment of OFG.

2 | METHODS

Patients from the allergy, immunology, or dermatology clinics of 10 different Italian reference centers[1] who were diagnosed with orofacial granulomatosis were included in the study. Data were retrospectively collected from medical records. Due to the absence of diagnostic criteria, diagnosis of OFG was based on clinical symptoms (persistent and/or recurrent enlargement involving the soft tissue of the oral and maxillofacial regions), exclusion of systemic granulomatous diseases (sarcoidosis, tuberculosis, IBD), and histological data (chronic non-caseous granulomatosis) if available. The study was approved by the Ethics Committee (protocol number 319/17—University of Naples Federico II, Naples, Italy) and conducted in compliance with the Helsinki Declaration.

An extensive review of the medical literature was conducted by searching all available clinical data up to April 2020 in several databases using a combination of MESH terms related to OFG (159 References), MRS (230 References), and GCM (24 References) back to the year 1965.

Among all, 91 full-text articles have been accessed. The remaining articles were excluded from the review because of inaccessibility of full-text article. The oldest article retrieved was published in 1965, the most recent in 2020.

3 | RESULTS

A total of 39 patients with OFG were recruited in 10 Italian centers between January 2018 and February 2020. Of 39 patients, 18 (46.2%) were males. The mean age at diagnosis was 45.3 (±17.5) years, whereas the mean age of onset was 41.9 (±17.26) with a mean diagnostic delay of 3.4 years (±3.6). None of the patients presented familial history for OFG or its variants. Among all the patients, 28.2% suffered from MRS. Almost all (97.4%) displayed persistent swelling of one or both lips, which was the most frequent localization and, in 11 (28.2%) of them, the lip was the only localization, suggesting the diagnosis of GCM. Additionally, 7 patients (17.9%) also presented oral aphthosis and 6 patients (15.4%) cervical lymphadenopathy. Histological evaluation was available for 34/39 patients (87.2%), and in 25 (73.5%), non-caseating granulomas were found. In the remaining 9 patients (26.5%), chronic non-specific inflammation was described, without pathognomonic diagnostic elements.

Eleven patients (28.2%) also presented neurological symptoms (hemicranias, dizziness). Eight (20.5%) patients complained gastrointestinal symptoms (diarrhea, abdominal pain), even in absence of IBD. Food or inhalant allergic sensitization was found in 9 patients (23.1%), by skin prick test (SPT) or specific IgE for food or inhalant allergens. In 5 out of these 9 patients, a history of clinical manifestations of allergic rhinitis or asthma was described. In 3 out of these 9 patients, no clinical manifestations of allergy were identified and raised specific IgE levels were found in the course of the diagnostic work-up. The remaining patient only displayed elevated total IgE levels in the absence of any clinical manifestation or specificity. Moreover, positive patch tests were found in 5 patients (12.8%), with only one patient referring symptoms (contact allergic dermatitis). Of these patients, one patient with allergic rhinitis and the patient with contact dermatitis also displayed increased levels of circulating eosinophils (690 and 750/μl, respectively). Among these five patients, one was positive to nickel and underwent elimination diet without any clinical response.

Six patients (15.4%) displayed positive anti-nuclear antibodies (titer>1:160); in this group, only one patient displayed a clinical history of stroke together with the positivity for antiphospholipid antibodies

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(lupus anticoagulant, anti-cardiolipin, anti-β2-glycoprotein I IgM) and reduced C3 and C4 levels.[9] The remaining 5 patients did not show any clinical sign or symptom suggestive of systemic autoimmune disease. Immunofluorescence pattern was explored only in 2 patients (one had nuclear and one had speckled pattern). Serum complement levels were normal in all patients, except the patient described above. Five patients (12.8%) presented hepatomegaly with normal liver function. Two cases presented periodontal disease (5.1%). Two patients received diagnosis of CD (5.1%) and one patient (2.6%) of sarcoidosis, suggesting secondary OFG. The clinical characteristics of the study population are shown in Table 1.

TABLE 1 Clinical features of our OFG patient cohort

Characteristics	Patients
Number, n (%)	39 (100)
Males, n (%)	18 (46.2)
Age at diagnosis, years	
Mean	45.3
SD	17.5
Age at onset, years	
Mean	41.9
SD	17.3
OFG subtypes*, n (%)	
MRS*	11 (28.2)
GCM*	11 (28.2)
Signs and symptoms, n (%)	
Lip swelling (one/both)	38 (97.4)
Neurological symptoms	11 (28.2)
Atopy	14 (35.9)
Gastrointestinal symptoms	8 (20.5)
Oral aphthosis	7 (17.9)
Cervical lymphadenopathy	6 (15.4)
Parodontal disease	2 (5.1)
Allergy work-up, n (%)	
Skin prick test	25 (64.1)
Positive	9 (36.0)
Patch test	18 (46.2)
Positive	5 (27.8)
Therapeutic options, n (%)	
Oral steroids	20 (51.3)
Responders (partial or complete)	14 (70.0)
Intralesional steroids	12 (30.8)
Responders (partial or complete)	8 (66.7)
Anti-H1 drugs	10 (25.6)
Responders (partial or complete)	0 (0)
Biological drugs	8 (20.5)
Responders (partial or complete)	5 (62.5)

MRS is defined as OFG with neurological involvement.
GCM is defined as OFG with only lip involvement.
*OFG was diagnosed according to criteria listed in the Methods.

Therapeutic approaches vary among the centers and are summarized in Table 2. We have classified the response to therapies in three possible outcomes: (i) good response when symptoms disappeared; (ii) partial response when patients had an improvement; and (iii) no response when the symptoms were unchanged after therapy. Intralesional steroids (triamcinolone acetonide, 40 mg/ml at 1 up to 4-week intervals) were used in 12 patients, and gave partial results in more than 60% of them. Systemic glucocorticoids (GCs) were the most commonly used drugs (51.3%) with good or partial results. Among oral steroids, betamethasone (1–2 mg/day) was used in 5 patients and gave the best results (100% good response). Prednisone (15–60 mg/day) and deflazacort (15 mg/day) were also used with variable results (50% partial responses). In 5 patients (12.8%) anti-TNF-α monoclonal antibodies were used. In more details, infliximab (5 mg/kg i.v. at 8-week intervals) or adalimumab (40 mg s.c. at two-week intervals) was administered, with partial response. The anti-IL-6 monoclonal antibody sarilumab (200 mg s.c. at two-week intervals) was used in a single refractory case without any therapeutic effect. In one patient, based on high circulating levels of total IgE, the anti-IgE monoclonal antibody omalizumab (300 mg s.c. monthly for 6 months) was used, with good clinical response but relapse upon drug discontinuation.[10] Lip reduction surgery was the choice for two patients with good and persistent results.[11] No response to anti-H1 drugs was observed.

4 | DISCUSSION

4.1 | Definitions, epidemiology, and clinical features

The term OFG was introduced in 1985 by Wiesenfeld to encompass the previously described disease entities of GCM and MRS.[12] The most frequent clinical feature of OFG is the swelling of the upper/lower lip, usually acute and painless (Figure 1A). It is intermittent in the early stages to become later persistent, but can also be recurrent or progressive.[13] When the swelling is pronounced, the lip starts to fissure on the midline (median cheilitis) and at the buccal angles (angular cheilitis). In addition to the typical labial involvement, OFG can affect oral cavity (mucosa of the cheeks, gums, palate, buccal floor, and tongue) as well as perioral, zygomatic, frontal, and eyelid regions (Figure 1B and C).[14,15] Among the most common oral features, typical deep-oral ulcers, affecting the vestibular and lip mucosa, rarely tongue and palate, can be found. Swelling of the labial and buccal mucosa typically appears like *"cobblestone."* Edema can also affect the gums giving them a granular appearance (Figure 1D). In most severe OFG cases, painful latero-cervical lymphadenopathy can be present.

GCM was first described in 1945 as a rare disorder characterized by persistent swelling of one (usually the upper) or both (rarely) lips. The initial intermittent swelling generally resolves spontaneously. However, after several recurrences the swelling becomes chronic, resulting in multiple granulomas, with aesthetic and functional deformities. Some patients report a burning sensation. Rarely, GCM appears

TABLE 2 Overview of the therapeutic options in the 39 OFG patients

	Treated patients					Responders	
Treatment	**N°**	**%**	**Drug**	**Dose**	**Duration**	**N°**	**%**
Intralesional steroids	12	30.8	Triamcinolone acetonide	40 mg/ml at 1- to 4-wk intervals	3–12 mo	8	66.7
Oral steroids	20	51.3				14	70
	10	50	Prednisone	15–60 mg/d	3–6 mo	5	50
	5	25	Betamethasone	1–2 mg/d	3- to 7-d cyclic administration	5	100
	2	10.0	Deflazacort	15 mg/d	3–6 mo	1	50
cDMARDs	6	15.4					
	3	50	Methotrexate	7.5–15 mg/wk	6–12 mo	3	100
	3	50	Sulfasalazine	1–2.5 g/dk	8–12 mo	0	0
Biologics	8	20.5					
	2	25	Infliximab	5 mg/kg at 8-wk intervals	1–4 yrs	1	50
	4	50	Adalimumab	40 mg at 2-wk intervals	3–6 mo	3	75
	1	12.5	Omalizumab	300 mg at 4-wk intervals	6 mo	1	100
	1	12.5	Sarilumab	200 mg at 2-wk intervals	3 mo	0	0
Antihistamines	10	25.6					
	4	40	Cetirizine	10 mg/d	1–3 mo	0	0
	3	30	Rupatadine	10 mg/d	1–3 mo	0	0
	1	10	Ebastine	10 mg/d	1–3 mo	0	0
Others							
Clarithromycin	1	2.6	Clarithromycin	500 mg bid	5- to 7-day cyclic administration	1	100
Minocycline	2	5.1	Minocycline	100 mg/d	1 mo	1	50
Doxycycline	2	5.1	Doxycycline	100 mg/d	3 mo	1	50
Montelukast	1	2.6	Montelukast	10 mg/die	2 mo	0	0
Tranexamic Acid	1	2.6	Tranexamic Acid	1500 mg/die	1 mo	0	0
Surgery	2	5.1				2	100

Abbreviations: bid, twice a day; cDMARDS, conventional DMARDS; d, day; mo, month; wk, week; yrs, years.

in association with systemic symptoms such as malaise, fever, and/or regional lymph node enlargement. Due to its rarity, GCM is quite neglected, with undefined incidence and prevalence.[16] Most of the literature suggests an equal sex distribution, but a higher frequency in females is also reported. GCM usually appears between 20 and 40 years of age and rarely affects children.[16] Rare familial cases have been reported. This disorder is considered a subset of OFG or an incomplete variant of MRS. Indeed, GCM may be the onset sign of MRS, followed by the development of the neurologic symptoms in 40% of cases.[16]

MRS is a rare neuro-mucocutaneous syndrome including orofacial edema, facial nerve paralysis, and plicate tongue. These three clinical entities can be present all together (complete form) or not (mono- or oligo-symptomatic MRS).[2] Symptoms usually appear in the second decade of life, without sex preference. The incidence is still unknown, and the diagnostic delay is estimated in about 10 years.[17] The onset of MRS generally occurs with the appearance of asymmetric and non-itchy orofacial edema. Rarely, orofacial swelling can be associated with genital, circumscribed, non-painful edema. Facial nerve paralysis occurs suddenly, is localized on the same side of the facial edema, and is clinically not distinguishable from Bell's paralysis.[18] It can be bilateral, partial or total, recurrent (in about 70% of patients), and persistent. Involvement of other cranial nerves (trigeminal, hypoglossal, glossopharyngeal, olfactory, vestibular) has been reported, leading to dysphagia, dysarthria, altered vision, and impaired eye motility.[19] If the fifth cranial nerve is affected, there can be hyperesthesia and migraine, or even damage to chewing muscles ("*masticatory atonia*") with limited mouth opening.[20] In this case, the finding of normal serum creatine kinase (CK) levels suggests that the damage is not attributable to myositis, but to muscular paralysis due to nerve inflammation instead.[20]

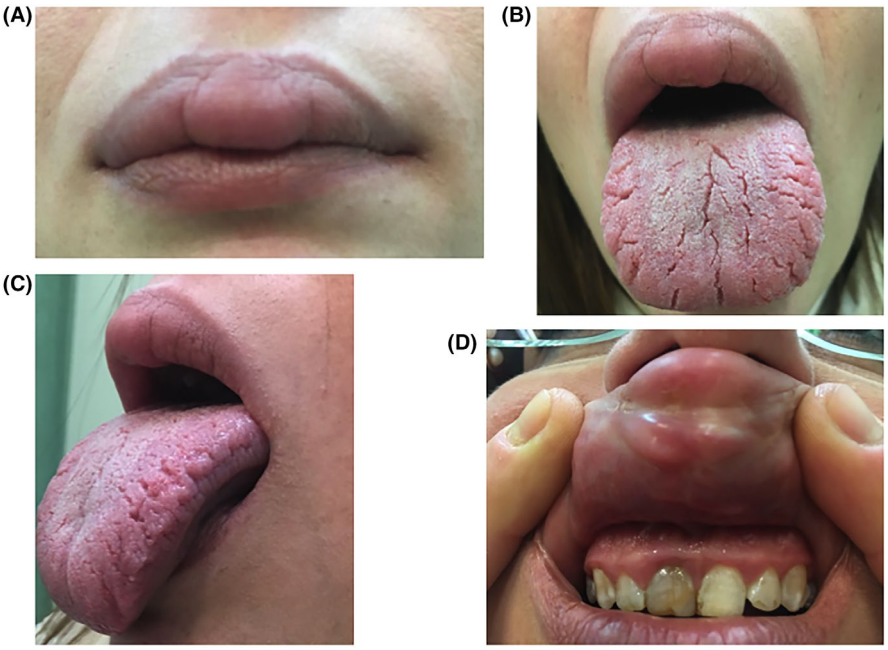

FIGURE 1 Persistent lip swelling (A), fissured tongue (B–C), and gingival hypertrophy (D) in a young female patient with OFG

4.2 | Pathogenesis, histological aspects, and differential diagnosis

The pathogenesis of the OFG is still unknown although a number of mechanisms have been hypothesized, including genetic predisposition, infectious, allergic, or immunological genesis.[2,3,21-23] The most common triggers for lip swelling are trauma and infections, but these are typically characterized by transient swelling.[1] The more persistent aspect of OFG can be mimicked by a number of different entities, summarized in Table 3. In particular, CD and sarcoidosis need to be carefully investigated.[4,6,7,24,25] Currently, there is no consensus on the consideration of OFG as an independent clinical entity from or an oral manifestation of CD. In our patient cohort, fecal calprotectin measurement and abdominal US were performed in all patients, even in asymptomatic patients. Endoscopy was reserved to patients referring gastrointestinal symptoms. Further studies are needed to better clarify the relationship between OFG and CD.[8] In some cases, the intestinal involvement can be paucisymptomatic compared with the oral manifestations and CD can be then diagnosed only following an intensive screening.[5] Therefore, underestimation of CD in our patient cohort could be due to the short follow-up of these patients. To this aim, an extensive clinical investigation of digestive and extra-digestive signs of CD is needed. A multi-disciplinary approach, involving a gastroenterologist, is advisable, and in selected cases, endoscopy with biopsy might be performed.

Histological analysis is useful, above all for incomplete forms of OFG, and is part of the differential diagnosis with other granulomatous disorders including cutaneous tuberculosis (TB), leishmaniasis, and leprosy, particularly in endemic areas.[16] The OFG-affected tissue typically shows sub-epithelial edema, increased number of dilated lymphatic vessels, granulomatous infiltrate and non-necrotic, non-caseous granulomas with lymphocytes in the center and large epithelioid cells on the periphery with or without multinucleated giant cells, perivascular mononuclear infiltration, in some cases with local fibrosis.[26] The edema is due to the lymphatic and vascular destruction by granulomas, with subsequent vascular inflammation. A typical histopathological examination of a lip biopsy from a MRS patient of our cohort is illustrated in Figure 2. These histopathological features are not always observed, and their absence should not formally exclude the diagnosis.[16] In our OFG patient cohort, histological evaluation was available for 87.2% of patients, and in 73.5% of them, non-caseous granulomas were found. In the remaining 26.5%, chronic inflammation was described, without striking elements. As already mentioned, there is no consensus about the usefulness of biopsy for diagnostic purposes, and in particular for the complete form of MRS, in which the diagnosis has often been merely clinical. This appears as a very confounding aspect and makes diagnosis non-univocal. In our opinion, however, histopathological analysis is always necessary to complete diagnosis and to exclude differential diagnostic alternatives, in particular infectious diseases. Although the histopathological features are not exclusive or specific for OFG, they strongly support the diagnosis.

In a Chinese case series of 16 patients with facial palsy in MRS, familial history was positive in about one third of the patients (31.3%).[27] However, none of the patients of our cohort presented familial history. In some cases, neuroimaging is helpful to identify edema and thickening of facial soft tissues, as well as inflammation of the cranial nerves. Encephalic computed tomography (CT) and/or magnetic resonance (MR) can support the diagnosis and exclude other diseases. Some studies reported increased levels of IgG into cerebrospinal fluid and serum of MRS patients, suggesting a possible immunological pathogenesis of the syndrome.

Apical periodontitis has been described in association with OFG.[21] In our patient cohort, periodontitis was diagnosed in 2

TABLE 3 Differential diagnosis of OFG and its variants

Disease	Differences from OFG
Crohn's disease	Intestinal involvement (mainly of terminal ileum). Histological aspects indistinguishable from OFG.
Sarcoidosis	Pulmonary, lymph node, cutaneous, salivary gland, neurological involvement. Rarely affects the oral cavity and lips
Histaminergic angioedema	Edema of the face, lips, tongue, larynx, or pharynx into a clinical picture of anaphylaxis. History of atopy. Antihistaminic drugs response. Identifiable trigger. Complete remission of symptoms between acute episodes
Hereditary angioedema	Complete remission of symptoms between acute episodes.
Cheilitis glandularis	Lip swelling with ulcers. Histology characterized by chronic inflammatory process, without granulomas, in minor salivary glands.
Tuberculosis	Lips rarely involved. Typical histological finding: caseous granuloma.
Granulomatosis with polyangiitis	Necrotizing granulomatous vasculitis of small vessels involving the upper and lower respiratory tract and kidney. It can also involve other districts such as the oral cavity (typical picture of gingival hyperplasia and gingivitis with strawberry gums).
Behçet's disease	Chronic-relapsing systemic vasculitis of small, but also medium and large vessels. Typically characterized by relapsing *aphthosis* (minor or major ulcers and herpetic ulcers), associated with genital ulcers, ocular manifestations (anterior and posterior uveitis, optic neuritis, retinal vein occlusion, retinal vasculitis), thrombophlebitis, and skin lesions (erythema nodosum).
Foreign body reaction	Identifiable to polarized microscope observation.
Granulomatous rosacea	Clinical diagnosis based on the specific primary and secondary criteria.
Fungal infection	Identification of pathogens with culture tests.
Leprosy	Identification of *Mycobacterium leprae* by culture tests.
Mucocele	Typical features distinguishable with imaging tests (CT, MR).
Amyloidosis	Histologic diagnosis through observation of the polarized light microscope after appropriate Red Congo staining.
Minor salivary glands tumors (microcystic adnexal carcinoma)	Typical features distinguishable with imaging tests (CT, MR) and histology.
Ascher syndrome	Congenital and characterized by the association of blepharochalasis and folding of the lip mucosa (usually upper) which resembles a double lip appearance. It is accompanied by other disorders (thyroid goiter, hypertelorism, ptosis, ogival palate, clinodactyly, etc.).
Thyroid orbitopathy	Eyelid swelling associated with a thyroid dysfunction (hyperthyroidism).
Bell's palsy	Absence of orofacial swelling and plicate tongue.
Morbihan syndrome	Chronic erythematous edema localized exclusively on the forehead, glabella, eyelids, and cheeks. It is considered a clinical variety or a complication of acne or rosacea
Trigeminal neuralgia	Absence of the MRS triad with pain as the dominant symptom.

out of 39 patients (5.1%), but not relevant benefit on OFG was obtained from its treatment. TB was ruled out in all patients, with the exception of one MRS patient with latent tuberculosis. However, histopathological examination excluded TB and the OFG did not benefit from the anti-TB therapy. In our cohort, 35.9% of the patients presented atopy, with food or inhalant sensitization. 15.4% of patients were positive for circulating antinuclear antibodies even in the absence of clinical symptoms of autoimmunity. However, no clear pathogenic link was evident with these conditions, and only descriptive association can be made.

4.3 | Therapeutic approaches

Although some rare spontaneous remissions have been described, most cases require one or more therapeutic agents. Several therapeutic strategies have been proposed, with no clear consensus. A summary of the published studies related to the therapeutic approaches is described in Table 4 and a summary of the therapeutic options used in our patient cohort is displayed in Table 2.

With regard to published data, restrictive diets were considered as first-line treatment, with good response to a cinnamon- and benzoate-free diet.[28] Interestingly, patch tests were not useful in

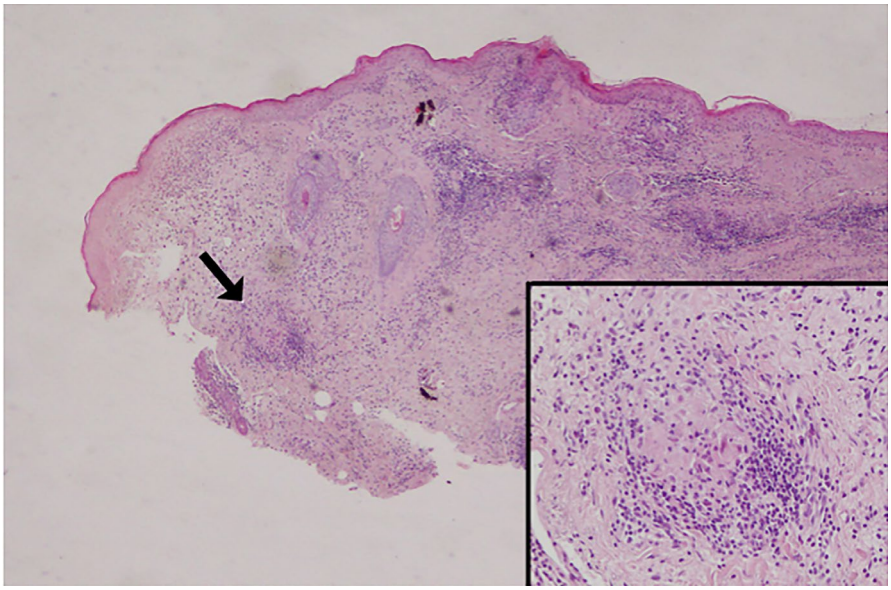

FIGURE 2 Histopathological examination of an incisional biopsy taken from the upper lip of patient with MRS showing chronic inflammatory infiltrates of submucosa and a small granuloma (arrow), consisting of lymphocytes, histiocytes, and epithelioid cells. The granulomas are shown at high magnification (400×) in the inset]

predicting the clinical response to the exclusion diet. Clinical improvement was evident within the first weeks. In absence of any significant improvement in 12 weeks, therapeutic alternatives were added and other allergens considered.[28,29] Campbell et al. conducted a study administering a diet without cross-reactive foods to patients with OFG and positive skin prick test (22 of 47 OFG patients) to silver birch, grass, mugwort, ragweed, and latex.[30] Among the fourteen patients that completed the 12-week observation period, two showed significant improvement and did not require any additional treatment.[30] However, the small number of patients and the poor results suggest the uselessness of this approach in the current clinical practice. In our cohort, no elimination diet was carried out with the single exception of the patient tested as positive to nickel by patch tests without, anyway, any clinical response. A perspective study with an extended allergy work-up by prick and patch test may better evaluate whether atopy plays a role in the pathogenesis of OFG and validate the effectiveness of the exclusion diet.

Many medical therapeutic options have been described such as GCs, immunosuppressants (azathioprine, methotrexate, thalidomide, tacrolimus), anti-TB agents (ethambutol, isoniazid), antimalarials (chloroquine), anti-leprosy drugs (clofazimine and dapsone), metronidazole, anti-TNF-α monoclonal antibodies (infliximab, adalimumab), sulfasalazine, antibiotics, and non-steroidal anti-inflammatory drugs (NSAIDs).[1,2,7,12,25,26,28-38]

Among these therapeutic options, GCs are the most used. Intralesional administration is considered the best choice because of the possibility to release high concentrations of the drug in the affected site, overcoming the *stratum corneum* and avoiding local side effects such as atrophy and hypopigmentation.[26,33,39] Usually, triamcinolone acetonide 10–40 mg/ml is used, in multiple affected sites for 2–3 weeks.[26] Intralesional administration once a week for 3 weeks (one cycle) also showed a decrease in disease severity scores at all post-treatment time points.[33] Intralesional triamcinolone acetonide was also administered in 12 out of 39 patients in our cohort, with good clinical result in more than 60%.

Systemic GCs with or without immunosuppressive agents can be used and show benefit on ulcers but less frequently on labial swelling and often a recurrence is observed after suspension.[1,25] In our cohort, systemic GCs were used in 51.3% of patients, with variable clinical response. Interestingly, all the 6 patients positive for the antinuclear antibodies displayed a good or partial clinical response to oral or intralesional GCs, suggesting that, even in the absence of any clinical history, autoimmunity should always be evaluated in OFG patients and that the presence of antinuclear autoantibodies could support the use of GCs. However, GC indication in OFG is limited by the paucity of available studies. Wider studies on large scale are needed to further clarify this aspect.

Interestingly, in a cohort of patients suffering from OFG alone compared to patients suffering from OFG and CD,[40] all treated with azathioprine (AZA), the proportion of patients responding to AZA with a diagnosis of CD/OFG was significantly higher compared to patients with OFG only. Factors predicting a need for AZA included a diagnosis of intestinal CD, sulcal swelling, sulcal ulcers, and upper lip involvement. The factor predicting response to treatment was a diagnosis of CD at 12 months of follow-up.[40]

The management of the facial nerve paralysis in the course of MRS is usually based on cycles of group B vitamin complex and systemic GCs.[22,41,42] For frequent and progressive facial paralysis unresponsive to medical therapy, an alternative is the surgical decompression of the facial nerve, which was not needed by any of the patient of our cohort.[43,44] Acupuncture and physical therapies were also reported.[41]

In a pediatric cohort of OFG patients treated with exclusive enteral nutrition using amino acid formula, good clinical response was shown to 6 weeks.[7] Effective use of low-level laser was described in a case of OFG with good clinical response.[35] Azithromycin was also used without clinical improvement.[31] Surgical cheiloplasty remains

TABLE 4 Published therapeutic approaches for orofacial granulomatosis

Ref	Diagnosis	N° of patients	Therapy	Outcome
Barry et al. (2005)	GCM	1	Infliximab	Good response
Gaya et al. (2006)	GCM	1	Adalimumab	Good response
Kauzman et al. (2006)	OFG	2	Penicillin and antihistamines	No Response
			Intralesional triamcinolone 40 mg/ml	Good response
	OFG+CD		Systemic GCs	Partial response
Kakimoto et al. (2007)	MRS	1	Infliximab	Good response
Peitsch et al. (2007)	GCM	1	Infliximab	Good response
Ozgursoy et al. (2009)	MRS	3	Systemic or intralesional GCs	Good response
Oudrhiri et al. (2012)	MRS	1	Intralesional betamethasone and doxycycline	Good response
Ruiz Villaverde (2012)	GCM	1	Adalimumab	Good response
Campbell et al. (2013)	OFG	22	Cinnamon- and benzoate-free diet, avoiding additional allergens	Good response in 2 out of 22
Elias et al. (2013)	MRS	9	Oral prednisone, metronidazole, intralesional GCs	Good response
Liu et al. (2013)	MRS	7	Systemic GCs	Good response
Ravindran (2013)	OFG	1	Intralesional triamcinolone + clobetasol	Partial response
Ruozhouo Liu (2013)	MRS	7	Systemic GCs, group B vitamins, acupuncture, physical therapy	Good response of facial palsy, no response of fissured tongue
Fedele et al. (2014)	OFG	22	Intralesional GCs	Good response
Shui feng et al (2014)	MRS	44	Decompression facial nerve, systemic steroids, group B vitamins, physical therapy	Good response
Simonsen et al. (2014)	OFG+CD	2	Infliximab	Good response
	OFG		Topical GCs	Good response
Stein et al. (2014)	MRS	1	Adalimumab	Good response
Vishwanath et al. (2014)	OFG	1	Intralesional triamcinolone	Good response
Zulin Tan et al. (2014)	MRS	15	Facial nerve decompression (9 patients)	Good response
			Prednisolone 1 mg/kg/d (6 patients)	Partial response
Jasinska et al. (2015)	MRS+MCTD	1	Chloroquine	Good response
Kuok et al. (2015)	MRS	1	Oral GCs	Partial response
Lazzerini et al. (2015)	OFG+CD	5	Oral prednisone 2 mg/kg/d	No response
			Infliximab + thalidomide 100 mg/d	Good response
			Oral GCs, antibiotics	No response
			Thalidomide	Good response
			Infliximab, oral steroids	No response
			GCs + AZA	No response
Mentzer et al. (2015)	OFG	60	AZA	Good response
Tan et al. (2015)	MRS	9	Facial nerve decompression	Good response
Mutalib et al. (2016)	OFG	10	6 weeks EEN + maintenance therapy	Good response
	OFG+IBD	19	Systemic GCs (4 patients)	NA
			Intralesional GCs (1 patient)	NA
			Targeted exclusion diet (2 patients)	NA
			6 weeks EEN (12 patients)	Good response
Badshah et al. (2017)	GCM	1	Infliximab	Good response
Innocenti et al. (2017)	GCM	1	Cheiloplasty+infliximab	Good response

(Continues)

TABLE 4 (Continued)

Ref	Diagnosis	N° of patients	Therapy	Outcome
Jovan Lalosevic (2017)	OFG	1	Azithromycin, topical GCs	No response
			Dexamethasone (1 mg/kg/die for a 3-day pulse)	Good response
Atkin et al. (2018)	OFG	5	Azithromycin 500 mg/die for 3 days/week	No response (only short term benefit)
De Moll et al. (2018)	MRS	1	Adalimumab	Good response
Espinoza et al. (2018)	OFG	2	Cinnamon- and benzoate-free diet, avoiding additional allergens	Good response
Georgesen et al. (2018)	OFG+CD+erythema multiforme	1	Oral GCs, antibiotics	Good response but relapse
			Methotrexate + valacyclovir	Good response
Kosovali et al. (2018)	MRS	1	Systemic GCs	Good response
Maaz B. Badshah (2018)	OFG	1	Infliximab	Good response
Marttala et al. (2018)	OFG+CD	1	Cinnamon- and benzoate-free diet combined with periodontal prophylaxis	Good response
Nettis et al. (2018)	GCM	1	Omalizumab	Good response
Cancian et al. (2019)	MRS	1	Antihistamines	No response
			Montelukast	No response
			Tranexamic acid	No response
			Prednisone 25 mg/die progressively tapered over few weeks or over few days	Partial response
Jacome-santos et al. (2019)	OFG	1	Low-level laser	Good response

Abbreviations: AGCM, granulomatous cheilitis of Miescher; AZA, azathioprine; CD, Crohn's disease; EEN, exclusive enteral nutrition; GCs, glucocorticoids; MCTD, mixed connective tissue disease; MRS, Melkersson-Rosenthal syndrome; OFG, orofacial granulomatosis; NA, not available.

the only effective solution for unresponsive cases,[11] and also in our patient cohort, it gave good results in two patients.

Interestingly, based on the increased circulating levels of total IgE even in absence of a personal history of allergy, one patient of our cohort was treated with omalizumab with good clinical response as also recently reported.[10] It was suggested that the effect of omalizumab was due to its anti-inflammatory effects as down-regulating the inflammatory cytokines IL-2 and IL-13. The local reduction in IL-2 in OFG lesions could be responsible for the down-regulation of IL-2 receptors on lymphocytes and the suppression of the inflammatory process.[45] Quite recently, the case of a patient with GCM coinciding with CSU-related recurrent angioedema was reported, successfully treated with dapsone and omalizumab.[46] These two were the only reports describing the use of omalizumab in OFG. Further studies on a large scale are needed to confirm this therapeutic effect and to better understand the mechanisms of action of anti-IgE monoclonal antibody in OFG. Isolated case reports describe the usefulness of anti-TNF-α agents in OFG.[12,32,34,36-38,47] In our cohort, two patients were treated with infliximab and three with adalimumab (12.8%). Only one patient did not show benefit, whereas one complete and three partial remissions were obtained, suggesting that anti-TNF-α strategy may be an efficient therapeutic alternative in non-responsive OFG patients. By contrast, in a refractory case, the anti-IL-6 monoclonal antibody sarilumab was used, with inconclusive results.

5 | CONCLUSIONS

In this report, we describe the clinical and therapeutic features of the first and largest OFG patient cohort described in Italy so far. Numerous reports have been published but are limited to case reports and small case series, with low evidence.

Efforts are needed to approach the following crucial points.

First, OFG and its variants are still neglected diseases with unknown etiology and pathogenesis. Our study highlights many unmet needs for the correct management of this disease. In the absence of an accepted classification, different variants of OFG are not uniquely identified. A clear OFG classification shared by the international scientific community is mandatory to correctly interpret the data that will be collected in the future studies.

Second, patients with OFG remain a challenge in clinical practice. Our data show that the diagnostic work-up is differently approached based on the single-center experience; in particular, the need of a histological confirmation of OFG diagnosis is a knot to untie.

As a third point, although different therapeutic approaches are available, no predictive biomarkers, diagnostic criteria, or severity scores are available to orientate the therapeutic choice. The heterogeneity of therapeutic approaches observed in our cohort is due to the lack of shared guidelines and evidence-based therapeutic

strategy: Development of controlled studies to properly treat OFG-related disability should be a goal for the future.

Finally, early diagnosis is pivotal to improve the patient quality of life and perspectives. In some cases, a misdiagnosed OFG can significantly impair the quality of life of the patients, due to aesthetic concerns, painful oral ulcerations, and additional symptoms such as neurological involvement.

We suggest that international registries should be created to enrich and share information between the different centers and endorse diagnostic and therapeutic guidelines. In this view, to improve our knowledge about this disease, we are currently working on a centralized informatics database aimed to providing the best diagnostic and treatment guidance for medical practice.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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