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ARTICLE

Oro-facial Granulomatosis

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Synopsis: Orofacial granulomatosis (OFG) is an uncommon chronic inflammatory disorder of the orofacial region. It is characterised by sub-epithelial non-caseating granulomas and has a spectrum of possible clinical manifestations ranging from subtle oral mucosal swelling to permanent disfiguring fibrous swelling of the lips and face. Etiopathogenesis is unknown. A range of systemic granulomatous disorders including Crohn's disease and sarcoidosis may cause orofacial manifestations that cannot be distinguished from those of OFG. Treatment of OFG has proven difficult and unsatisfactory, with no single therapeutic model showing consistent efficacy in reducing orofacial swelling and mucosal inflammation.

Key Points:

- Orofacial granulomatosis (OFG) is an uncommon granulomatous disorder of the orofacial tissues. Disease hallmarks include development of disfiguring labial and/or facial enlargement and intra-oral mucosal swelling and ulceration. Etiopathogenesis remains unknown.
- Crohn's disease, sarcoidosis and a range of other systemic disorders can present orofacial features similar to those of OFG. However, a strict case definition of OFG requires the exclusion of concomitant systemic granulomatous disease.
- A small subgroup of OFG patients, especially those with disease onset during childhood, will eventually develop intestinal Crohn's disease or, more rarely, sarcoidosis.
- Management of OFG is challenging and not evidence-based. Prolonged anti-inflammatory and immune-modulatory systemic therapy is usually needed to obtain long-term control of severe orofacial swelling and inflammation. However intralesional corticosteroid therapy may provide notable long-term remission with no need of prolonged treatment.
- The vast majority of OFG patients on therapy will eventually experience a variable degree of reduction in clinical manifestations

Introduction

Orofacial granulomatosis (OFG) is an uncommon chronic inflammatory disorder that typically affects the soft tissues of the orofacial region (1). It is histopathologically characterised by sub-epithelial non-caseating granulomas and has a spectrum of possible clinical manifestations ranging from subtle oral mucosal swelling to permanent disfiguring fibrous swelling of the lips and face (2–6). Painful oral ulceration and neurological manifestations to the head and neck region can also occur (3–5). The first cases of a disorder causing recurrent/chronic orofacial swelling were initially reported in the nineteenth century (Wiesenfeld et al. 1985; James et al. 1986); eventually Melkersson (9) and Rosenthal (10) described the association between recurrent/chronic orofacial oedema, facial palsy and fissured tongue (*lingua plicata*). The term Melkersson-Rosenthal syndrome (MRS) was therefore introduced to describe individuals with the full triad of manifestations whereas those with only labial swelling were referred as having cheilitis granulomatosa (Miescher's cheilitis). In 1985 Wiesenfeld *et al* introduced the term orofacial granulomatosis (OFG) to encompass both MRS and Miescher's cheilitis (Wiesenfeld et al. 1985). Over the years a number of systemic granulomatous disorders (including Crohn's disease, sarcoidosis, leprosy, tuberculosis, chronic granulomatous disease and possibly deep fungal infections have been reported to cause orofacial manifestations (12) similar to those of OFG. It remains

controversial whether it is appropriate to refer to them as OFG. The authors of the present paper define OFG as an idiopathic granulomatous disease limited to the orofacial tissue, namely affecting individuals who do not show any evidence of previous or concomitant systemic granulomatous disease as per clinical, radiological, endoscopic, or serological investigations; diagnosis of idiopathic OFG remains therefore one of exclusion (3,5,6,13). As it is well established that some of these patients would eventually develop additional extra-oral/facial manifestations of a systemic granulomatous disease (e.g. colonic Crohn's disease), we suggest that their diagnosis should be at that point revised and re-termed (e.g. from OFG to oral and colonic Crohn's disease). This classification has a pragmatic clinical relevance, as individuals with OFG limited to orofacial tissues would benefit from therapeutic interventions and monitoring that are significantly different from those with a systemic granulomatous disease. Orofacial granulomatosis is an uncommon disease. No reliable epidemiological data are available as most cases series report small single-centre groups of patients (1). There remain few studies describing case series of 100 or more OFG patients, which however represent retrospective analysis of cohorts that are often heterogeneous (including patients with Crohn's disease) and observed during two or more decades (1,14). Orofacial granulomatosis seems to have no specific ethnic predilection, and most authors report that both genders are equally affected (1,15). The disease occurs by the end of the third decade of life in the vast majority of reported patients (1).

Orofacial granulomatosis can cause adverse effect upon the quality of life of patients due to disfiguring chronic orofacial swelling, painful oral ulceration and occasional neurologic involvement (16). Treatment of OFG has proven difficult and unsatisfactory, with no single predictable therapeutic model showing consistent efficacy in reducing orofacial swelling and mucosal inflammation (17).

The aim of the present paper is to present a comprehensive review of available literature about etiopathogenesis, clinical manifestations, prognosis and management of OFG.

Etiopathogenesis

Although a number of possible causative factors have been associated to OFG (13), the exact etiopathogenesis remains unknown. Existing literature has typically focussed upon the role of (i) delayed hypersensitivity to food substances, food preservatives, or dental materials, (ii) microbial infections and (iii) inflammatory/immunological factors (13). Recent findings regarding the immunopathogenesis of granulomas in Crohn's disease (18) and other rare granulomatous disorders (19,20) could indicate that similar defects of the innate immunity may also play part in the etiology of granulomas of OFG (21–23). Relevant studies are ongoing (24).

Hereditary and genetic predisposition:

There is no adequate data in the literature that supports that OFG has a definite genetic background (23,25). Reports of hereditary cases remain scarce and studies have not found any convincing robust HLA association (26,27) in OFG patients versus population controls.

Inflammatory/immunological factors:

Characterisation of granulomatous inflammation of OFG has lead to conflicting and inconsistent results. It remains unclear whether lesional T cells of OFG represent clonal expansion as a result of chronic antigen stimulation (23,28,29). Studies on the expression of

cytokines and chemokines in OFG lesions have found a predominant Th1-mediated immune response (23,30).

Hypersensitivity reactions:

A wide range of hypersensitivities have been reported in OFG patients including dental restorative materials (31,32), toothpastes and other dental hygiene products (33,34), cocoa and chocolate (33,34), cinnamon compounds, carvone, carbonyl piperitone, aspartate (33,35–39), carmosine and sun yellow dye (35), monosodium glutamate (35,40), benzoates (35,37–39,41,42) and tartrazine (41). Cinnamon and benzoate compounds have been suggested to be most common triggers (33–35,38,41,42). A potential role of hypersensitivity in OFG pathogenesis seems to be supported and confirmed by patient's history of symptoms aggravation associated with contact or ingestion of one or more of the above triggering factors, positive response to elimination diet, and in some cases positive patch testing (23,32). Further, a recent paper has reported OFG patients to have a higher prevalence of allergy than the general population as demonstrated by their medical history, skin prick test, and serum IgE (43). Nevertheless, other studies have failed to find convincing evidence of sensitisation to foods, additives or contactants in OFG patients (44). Also outcomes of avoidance diet remain controversial as they vary from 14% (14,45) to 70% (46) and seem not to correlate with patch testing results (46). It is possible that delayed hypersensitivity mechanisms may have a pathogenetic role in a small sub-group of OFG patients.

Microbial factors:

Several authors have investigated the potential role of microbial agents in triggering the immune response of OFG, including *M. tuberculosis*, *M. Paratuberculosis*, *Saccharomyces Cerevisiae*, *Borrelia burgdorferi*, *Candida albicans*, and *Streptococcus mutans*. Although some studies have reported the presence of *M. tuberculosis* RNA in OFG samples (47) and raised IgG antibody titers to the mycobacterial stress protein 65 (48) in OFG patients' serum, there remains little credible evidence to support a role of any of these agents in the aetiopathogenesis of OFG (27,49–52).

Clinical presentation

Disfiguring lip swelling remains the clinical hallmark of OFG and the most common reason for which OFG patients seek medical attention (53). Other possible clinical manifestations include swelling and ulceration of the oral mucosa, swelling of facial (other than labial) tissues, and neurological manifestations (3,54). It is probable that OFG represent a disease with a spectrum of severity that ranges from localized granulomatous inflammation of the lips, through orofacial swelling with mucosal ulceration to a disease with additional neurological deficit (3,55–57). Available literature indicates that clinical manifestations at disease onset can be highly variable and multiform, although permanent disfiguring labial and/or facial swelling eventually develops in nearly all affected individuals.

Labial swelling

Available literature clearly shows that labial enlargement is the most common feature of OFG, affecting more than 90% of patients (5). Lip enlargement is typically recurrent and oedematous in the early stages of the disease, with each episode lasting few days or weeks. (58–60). During the course of the disease and after a number of recurrent episodes the swelling of the lips typically becomes persistent, firm and indurated, assuming the characteristics of a granulomatous disorder (5). Lip fissuring, exfoliation and impetiginisation can be associated, especially in severe cases, and intraoral labial mucosa may become

erythematous and granular (5,59). The peri-oral skin may become erythematous and exfoliated and some patients may develop angular cheilitis (61). There is no site predisposition for the labial swelling although it may be slightly more common on the lower lip (3,5,7,62). The swelling rarely causes difficulties in speech or drooling (54).

Facial swelling:

Swelling of non-labial facial tissues has been described in OFG patients, sometimes in absence of lip enlargement or other clinical manifestations, and can vary in severity. Patients can develop recurrent or persistent enlargement of zygomatic, frontal, peri-orbital or chin/submental region (3,63), as well as the cheek and eyelids, which represent a diagnostic challenge as these are not favourable areas to obtain a biopsy specimen (3). Indeed blepharitis granulomatosa (or granulomatous blepharitis) it is likely to represent OFG-like disease (64,65). Swelling of submandibular and/or cervical areas due to persistent lymph node enlargement can arise in about 25% of OFG individuals (5,54).

Intra-oral manifestations:

Generalised swelling of the buccal and or labial mucosa gives rise to a cobblestone-like appearance (54), a common intra-oral features of OFG (66), particularly in the posterior buccal mucosa (54,55). Localised mucosal swelling manifest as discreet painless tags typically affect the vestibular buccal and labial mucosa or floor of the mouth (“stag-horning”) (5). Deep chronic linear ulcers with raised margins can arise in the buccal and/or labial sulcus and are often associated with significant pain (5). Less commonly flat and circular aphthous-like ulcers can arise on any oral mucosal surface. Pyostomatitis vegetans, which manifests with yellowish, linear pustules on the background of mucosal erythematous “snail track ulcerations” has also been described, although the vast majority of reports refer to individuals with evidence of inflammatory bowel disease (Crohn’s disease) (4,67–70). Painless gingival swelling independent of plaque and calculus deposits may occur in up to one third of patients with OFG (2,6,71,72). The swelling can affect the attached and/or free gingivae, be localized or generalized, and is often associated with erythema and superficial “granular” appearance (2,3). Generalised erythema/inflammation of the oral mucosa is uncommonly described as a separate intraoral feature of OFG (73) possibly because it usually develops in association with either manifestation including cobblestoning and ulceration. The tongue may have superficial fissures that are most pronounced on the lateral aspects of the dorsum (54). The fissuring may rarely cause food accumulation leading to alteration in taste, oral malodour and a local burning sensation (71,74). Fissuring of the tongue has been inconsistently associated with neurological manifestations (74).

Neurological manifestations:

A subgroup of patients with OFG may have lower motor nerve facial palsy at some point in the disease course (71,75). Granuloma formation or inflammation within the course of the main stem of the facial nerve is the most probable cause for the palsy (54). The exact prevalence of facial palsy in OFG is unclear, but studies report a very wide range of 8-57% (3,11,42,76). The palsy can be complete or partial but is typically unilateral. The palsy can occur before, with or after (sometimes months to years) the facial swelling (77). It also may be accompanied by otalgia and/or changes in hearing and taste (65). Complete recovery of nerve function is usual but some residual weakness can occur (75,78,79). Facial palsy can be considered as a feature of Melkersson-Rosenthal syndrome when associated with lip swelling and fissured tongue, although most clinicians now categorize Melkersson-Rosenthal

syndrome as a sub-type of OFG. A number of less common neurological manifestations have been reported to develop in up to 30% of OFG patients (2,3,7,76,79). These include blepharospasm, migraine-like headache, hypogeusia, glossodynia, hyperacusia, lacrimation and sweating (80,81). Relevant pathogenetic mechanisms remain unknown.

Clinical manifestations of early and advanced disease

Labial swelling is traditionally indicated as the most common clinical feature of OFG and was previously reported as being the most frequent manifestation at disease presentation. However, a number of authors have more recently suggested that OFG can in fact present with multiple, temporary and variable clinical features affecting oral mucosa, gingivae, facial tissues and the craniofacial nervous system (3), and that different clinical manifestations can develop at different time points during the course of the disease (2,3). Zimmer et al (1992) reported that labial swelling was the initial disease manifestation in only 43% of their 42 patients but this percentage increased to 74% during the course of the disease. Moreover, the overall number of clinical manifestations increased during the years as the percentage of patients with facial swelling increased from 26% to 50% and those with facial palsy from 19% to 33% (2). Mignogna et al (2003) reported that about half of their 19 OFG patients (9/19) had an “atypical” disease onset characterized by the absence of labial swelling, which however developed in seven of these nine patients at later stage. Al Johani et al studied a cohort of 49 OFG patients and confirmed that OFG present with lip swelling in only 50% of cases, whereas the remaining individuals had intra-oral or neurological manifestations in absence of labial or facial swelling (5). They also reported that the vast majority of patients eventually developed a variety of additional features of OFG, with nearly all affected individuals (>90%) ultimately developing lip/facial swelling (5).

Systemic association

Considering the strict definition and nomenclature that the authors of the present review have adopted, the concomitant presence of orofacial and other systemic manifestations of a specific and well-characterised generalised granulomatous disorder (e.g. Crohn’s disease or sarcoidosis) should exclude the diagnosis of idiopathic OFG. Indeed, as mentioned above, a diagnosis of “true” idiopathic OFG would require that detailed medical history, clinical assessment and comprehensive investigations are performed so to rule out the presence of these disorders and confirm that disease is limited to the orofacial tissues (23,25,60). Nevertheless, potential associations with systemic disease can still exist in patients with idiopathic OFG.

Subsequent development of systemic granulomatous disease

It is well described that a sub-group of OFG individuals would eventually develop manifestations of systemic disease, typically intestinal Crohn’s disease or respiratory/multi-organ sarcoidosis, even if at the moment of initial assessment there was no clinical, serological or radiological evidence of any relevant extra-oral abnormality (59,73,82,83). As discussed, it would be sensible at that stage to re-label these cases as, for example, having oral and intestinal Crohn’s disease or oral and respiratory sarcoidosis rather than maintaining the nomenclature of OFG in association with Crohn’s disease or sarcoidosis. It is difficult to predict which OFG patients will eventually develop extra-oral manifestations of a granulomatous systemic disease, although the vast majority of them are believed to have disease that will remain limited to the orofacial tissues. Campbell et al reported that only 20% of OFG patients followed-up in their cohort subsequently developed “true” symptomatic

Crohn's disease (59). They also confirmed previous observations that childhood onset of OFG carries at higher risk of subsequent Crohn's disease development (61,84). There is no convincing evidence that any particular clinical manifestation or haematological/histological feature in OFG patients might be predictive of future Crohn's disease development, including early asymptomatic intestinal inflammation (see below).

Several cases of multi-systemic sarcoidosis developing in individuals with disease onset limited to the orofacial region have been reported (85). Similarly to Crohn's disease, there remains no reliable clinical feature or test to predict development of systemic sarcoidosis in individuals with OFG-like disease, with the possible exception of raised serum angiotensin converting enzyme (sACE) levels (85).

Concomitant intestinal inflammation of unclear clinical significance

A variable portion of OFG individuals have been reported to show concomitant endoscopic and histological features of intestinal inflammation in absence of specific gastrointestinal symptoms and of unclear clinical significance. Both Scully et al in 1982 and Sanderson et al in 2005 reported evidence of intestinal inflammation in subgroups of OFG patients with no notable history of gastrointestinal symptoms. (34,45,73,86–89). The former study used rigid sigmoidoscopy and barium radiology on 19 patients and reported evidence of likely intestinal Crohn's disease in 37% of cases, (82) whereas the latter used flexible endoscopy and biopsies, and found discrete granulomatous intestinal inflammation (but no convincing evidence of Crohn's disease) in 54% of the 35 patients studied (73). Clinical significance of asymptomatic gut inflammation in these sub-groups of OFG patients is unclear. Unfortunately these studies were not followed by a long-term observation and it is unknown whether the presence of discrete intestinal inflammation in OFG patients might be predictive of subsequent development of symptomatic full-blown Crohn's disease.

Allergy

It has been found that an history of IgE-mediated clinical allergy in the form of hay fever, eczema, asthma, or oral allergy syndrome can be observed in up to 80% of OFG patients compared with 15-20% of the general population (34,43,86–89). The most frequent skin prick testing-confirmed sensitizations were to grass, silver birch, ragweed, mugwort, latex and pollens (43,45). The clinical significance of IgE-mediated atopy in OFG patients is unclear as dietary avoidance of cross-reactive foods failed to demonstrate significant improvements in the vast majority of patients (45). Patients with OFG have also been described to have patch test-confirmed delayed-type hypersensitivity to a number of food substances and additives including wheat, dairy products, chocolates, eggs, peanuts, cinnamaldehyde, carbone piperitone, cocoa, carvone, carmosine, sun yellow dye, monosodium glutamate, benzoate, and cow's milk (23). Delayed hypersensitivity to some dental materials including amalgam, mercury, gold and cobalt has also been reported (23). Elimination diets and replacement of the relevant dental material have been reported to improve clinical manifestations by some, albeit not all, authors (23,44). Significant limitations of available studies about dietary manipulation include concomitant use of immunosuppressive agents, open label design with no controls, and surprising lack of correlation between patch testing result and dietary outcome (59,88).

Evaluation and management

Diagnosis and assessment

Diagnosis of OFG requires (i) the presence of relevant oro-facial clinical features, and (ii) the exclusion of systemic disorders causing similar manifestations through detailed medical history and serological, radiological, and/or endoscopic investigations (where clinically justified). Histopathological confirmation of non-caseating granulomas is not a required criterion, although it may provide useful information contributing to exclude other causes of granulomatous inflammation (Table 1). There is no consensus with respect the most appropriate measure or instrument to assess OFG disease severity/activity and monitor response to treatment. Most authors have adopted a pragmatic, although highly subjective, patient and/or clinician-centred assessment of swelling and inflammation, and some have used standardised clinical photographs to support patients' and clinicians' judgement (6). Disease severity/activity scores have been suggested by different groups (53,73) but are limited by a lack of adequate validation. A newly developed quality of life questionnaire known as COMDQ (Chronic Oral Mucosal Diseases Questionnaire) was demonstrated to be a valid and reliable measure to assess quality of life in patients with chronic oral mucosal diseases including OFG (90). However the number of OFG patients included in COMDQ validation study was very small, and further confirmatory evidence is needed. Chiandussi et al have proposed an objective method for assessing lip size and treatment-related morphological changes based on lip impressions and measurement of related plaster models (91).

Management

The principal goal of OFG therapy is to lessen cosmetically undesirable orofacial swelling and control painful mucosal ulceration, however treatment may not be always needed if symptoms and/or signs of OFG are mild. A number of treatment strategies have been reported during the last 3 decades, but relevant outcomes remain variable and often unpredictable. The overall evidence regarding the effectiveness of available therapeutic options is not robust due to the lack of randomised control trials and use of inconsistent, often subjective, outcome measures. Lack of multicentre collaborations recruiting large groups of OFG patients adds further limitations to available data.

Available literature suggests that the treatment of the disfiguring orofacial swelling of OFG has proven exceedingly difficult and remains unsatisfactory (17,53). Immunosuppressants, tumour necrosis factor alpha inhibitors and other agents, as well as surgical cheiloplasty have been used as single or combined therapy with some positive, although overall inconsistent, results in a variety of cases reports and small case series (17). Similarly, the encouraging results of a benzoate- and cinnamon-free diet reported by White *et al.* have never been replicated by other groups and need further research. Recently a 3-week regimen of intralesional triamcinolone acetonide was reported to provide long-term reduction of disfiguring orofacial swelling of OFG.

Topical corticosteroid and immunosuppressants

Topical corticosteroids and tacrolimus applied directly onto the lips and oral mucosa have been reported to induce reduction of the labial swelling and oral ulceration in small numbers of patients (92,93), although benefits are often temporary and disease can quickly recur (5,54). Topical application of corticosteroid and tacrolimus is reported as generally safe with a low incidence of adverse side-effects including oral candidosis, mucosal burning sensation, sore throat, transient taste disturbance, mucosal staining, and headache (94–99).

Intralesional corticosteroids

Intralesional injections of corticosteroids in the treatment of orofacial swelling of OFG were originally introduced in 1971 (100). Initially low concentration triamcinolone acetonide (10mg/mL) was used, requiring multiple sessions (12 to 20) of injections at approximately 2 week intervals in order to obtain a favourable, although transient, clinical response. Local block anaesthesia at each session was required because of significant pain associated with injecting 1-2mL of triamcinolone into affected tissues (101,102). In 1992, Sakuntabhai et al suggested using a higher volume of triamcinolone in order to increase efficacy, reduce the number of treatment sessions, and attempt long-term swelling remission (103,104). Under mental and/or infraorbital nerve blocks with 2% lidocaine, they injected a high volume of triamcinolone acetonide (mean 6mL) into the affected lip. Even if swelling increased immediately after the injections, their regimen showed to be effective and led to nearly complete clinical remission and a long-term swelling-free period (10-12 months). Intralesional therapy was further modified in subsequent years with the introduction of highly concentrated triamcinolone acetonide (40mg/mL) (105). This formulation allows injection of a high dose of triamcinolone within a reduced drug volume, thereby increasing efficacy, reducing associated pain and avoiding the need for anaesthetic block (105,106).

The largest cohort of OFG patients managed with triamcinolone injections was reported by Fedele et al (107). They described the long-term outcomes of a homogeneous group of 22 OFG patients who had been managed with a standardised therapeutic regimen of triamcinolone injections (107). The treatment led to a significant reduction in orofacial swelling, with the majority of patients showing no disease recurrence after a single course of therapy for up to 4 years. Those who experienced swelling recurrence responded well to a second course of therapy. Of note, the vast majority of patients reached swelling-free status at 2-week time point after the first course of therapy; all patients did so at 1-month time point. Adverse side effects of intralesional therapy are uncommon and include local hematoma (100,104), skin atrophy, mild transient swelling of the lip (103) hypo/hyper-pigmentation (105) and rarely candidiasis (56).

Systemic corticosteroids and immunosuppressants

Short courses of moderate dosage prednisolone (25-50 mg/day; 0.3-0.7 mg/kg/day) or deflazacort (108) (30-60 mg/day; 1.2:1 therapeutic dosage ratio to prednisolone) can quickly reduce orofacial swelling of OFG (55–57), but benefits are typically short-lived and followed by disease recurrences. Long-term corticosteroid therapy is characterised by several adverse side effects and therefore systemic immunosuppressants are likely to represent a safer options in the long-term management of OFG. A recent report demonstrated a significant improvement in lip swelling and erythema after one month of mycophenolate mofetil (MMF) 500mg twice daily, with sustained benefits and no notable toxicity after 1 year of therapy (109). Although azathioprine is commonly used by many clinicians to achieve long-term immunosuppression and swelling reduction in OFG patients, there remain no papers reporting in detail the use of relevant therapeutic regimens and their outcomes (110,111).

Anti-tumour necrosis factor (TNF) agents

Thalidomide, infliximab and adalimumab have been occasionally used in the therapy of OFG in small groups of patients with variable outcomes. Low-dose thalidomide (20-100 mg daily) has been reported to induce notable reduction in OFG-related facial swelling (92,112–115)

even after previous failure of other topical and systemic immunosuppressant therapy (92). The main limiting factor of thalidomide therapy is represented by its toxicity: in addition to its teratogenicity, thalidomide can cause sensory and motor neuropathies, and skin rash (92,113,116,117). Infliximab and adalimumab have been used in small groups of patient with OFG and with oral manifestations of intestinal Crohn's disease (118,119). Available evidence suggests that infliximab can provide good-short term response in the majority of OFG patients (up to 70%), however recurrences are common with only one third of patients being still responsive after 2 years (118,119). It has been suggested that patients failing infliximab therapy may benefit from adalimumab (118,119). Because of the association with potentially serious adverse effects, which include infusion reactions, infection and increased risk of malignancy (118) use of infliximab and adalimumab in OFG should mirror that for intestinal CD, that is, severe disease and intolerant or resistant to standard systemic therapy.

Diet modification

A number of studies have attempted treatment of OFG via elimination of potential allergens from the diet of affected patients. In addition to multiple case reports of patch test-proven hypersensitivity to a single antigen and relevant dietary avoidance (23), an UK group have developed three separate dietary interventions aimed at reducing orofacial swelling and other intra-oral manifestations of OFG: a cinnamon- and benzoate-free diet (88), a dietary avoidance of cross reacting foods in OFG individuals with positive skin prick test to silver birch, grass, mugwort, ragweed and latex (45), and a low phenolic acid diet (120). Although the authors claim that some of these interventions can reduce orofacial inflammation of OFG in up to 70% of cases, there remains little robust evidence regarding their actual effectiveness due to methodological limitations of available studies.

Anti-leprotic agents

Dapsone and clofazimine that have been occasionally reported to reduce the orofacial swelling of OFG (55,121–124). In one study, long-treatment with low-dosage clofazimine (400-700mg weekly for 3–11 months) led to complete remission in 5 of 10 treated patients and partial improvement in a further 3 patients (125). There are only few published cases of dapsone therapy in OFG, with relevant results ranging from complete relief to ineffectiveness (63). It seems that anti-leprotic agents may be more effective during the early stages of the disease (121).

Miscellaneous drugs

There have been reports of small number of patients with OFG having clinical benefits with methotrexate (126), sulphasalazine (127), lymecycline (128), minocycline (129), or 5-amino-salicylic acid (130), metronidazole (115,131–133) hydroxychloroquine (122), and various combinations of these agents with systemic, topical or intralesional corticosteroids.

Surgery and low-level laser therapy

OFG patients with long-standing and disfiguring fibrotic swelling that has proven to be unresponsive to treatment may benefit from surgical correction. Relevant plastic surgery procedures include cheiloplasty, commissuroplasty, facial liposuction and tangential resection of labial mucosa, submucosa, and muscles (134). It has been recommended that surgical correction of OFG should be undertaken during inactive phases of the disease (25,122), and possibly in association with perioperative oral or intralesional corticosteroid therapy (135–137). The long-term benefits of surgery are largely unknown although

recurrence of the labial swelling following surgery has been reported (138,139).

Merigo et al reported complete remission of labial swelling with the use of low-level laser therapy (LLLT) in one OFG patient who had previously failed to respond to topical and systemic corticosteroid and immunosuppressive therapy (140). Low-level laser therapy is believed to have anti-inflammatory and wound-healing properties (140). Of note, clinical remission was maintained for two years after treatment (140).

Psychological support

When orofacial enlargement of OFG becomes persistent and aesthetically unacceptable, typically in cases of absent or partial response to therapy, psychological support and counselling may be beneficial in developing coping mechanisms and improving quality of life (127). However there are no studies investigating potential benefits of psychological interventions in OFG individuals.

Clinical outcomes

Although variable and multiform in its early stages, the natural history of OFG is ultimately progressive, and permanent disfiguring labial and/or facial swelling eventually develops in nearly all affected individuals (53). Spontaneous resolution is exceptionally rare and the vast majority of patients would eventually require medical treatment. The long-term prognosis of OFG individuals is largely unknown. Al-Jahani et al studied the long-term clinical outcomes of 49 patients with OFG who received a wide variety of treatments and reported that facial swelling of OFG tends to improve over time in those who are on therapy, with approximately 78% of patients showing some reduction in their clinical manifestations. However, only 46.8% eventually experienced complete resolution of orofacial swelling (6). Historically a variety of different topical and/or systemic agents have been used during the long-term management of OFG patients with a variable incidence of development of new manifestations, lack of response, and adverse side effects (6). However, more recent and better designed studies seem to suggest that some single treatment modalities could effectively provide long-term control of the disease, as in the case of intralesional corticosteroid injections (53). A summary of clinical outcomes of available interventions is provided in (Table 2).

Conclusion

Orofacial granulomatosis is an uncommon inflammatory disorder that typically affects children and young adults and causes disfiguring facial swelling and painful oral ulceration. Although a strict case definition of OFG requires the absence of any systemic granulomatous disease, an unpredictable subgroup of individuals with OFG limited to the orofacial tissues would eventually develop intestinal Crohn's disease or, more rarely, sarcoidosis. A significant number of OFG patients show evidence of concomitant IgE-mediated allergy and delayed-type hypersensitivity to a number of food and other antigens, although relevant role in etiopathogenesis and therapy remains unclear. Management of OFG is often difficult and not evidence-based. Mild cases would benefit from topical immunosuppression whereas long-term anti-inflammatory and immunosuppressive agents are needed to control more severe facial swelling and painful oral ulceration. Intralesional corticosteroid therapy may provide notable long-term remission with no need of prolonged treatment. It seems that the vast majority of OFG patients on therapy would eventually experience a variable degree of reduction in orofacial swelling.

Tables:

Table 1. Diagnostic investigations and criteria of orofacial granulomatosis

Investigations	Results
Full blood cell count	Should be normal
Hemoglobin	Should be normal
Serum angiotensin converting enzyme levels*	Should be normal
C-1 esterase inhibitor levels ^y	Should be normal
Serum iron and transferrin	Should be normal
Tuberculin skin test (when clinically justified)	Should be negative
Chest radiography (when clinically justified)	Should be normal
GI endoscopy/histopathology ^z	Should be normal; if inflammatory changes are present, Crohn disease should be excluded
Histopathology I: dilated lymphatics, edema of corium, slight fibrosis, with/without multiple noncaseating granulomas with Langerhans giant cell and lymphocytes	Should be present [§]
Histopathology II: PAS reaction and Ziehl-Neelsen stain (when clinically justified)	Should be negative
Polarized light microscopy: identification of birefringent foreign-body material (when clinically justified)	Should be negative

GI: Gastrointestinal; PAS: periodic acide-Schiff.

*To be performed when there are clinical features compatible with potential diagnosis of sarcoidosis.

^yTo be performed when orofacial swelling is recurrent and edematous without signs of persistent tissue fibrosis.

^zTo be performed when clinical or laboratory features increase suggestion of GI inflammatory disease.

[§]Absence of histopathological features does not exclude orofacial granulomatosis diagnosis if clinical features are compatible.

Table 2. Clinical outcomes of OFG therapy

Therapy	Clinical outcome	Level of evidence
Topical agents:		
Corticosteroids (3, 141, 142)	Effective in managing moderate intra-oral lesions and mild labial swelling.	D
Tacrolimus (93)	Marked improvement in lip swelling. Benefits can be transient.	
Intralesional corticosteroids		
Low volume triamcinolone acetonide [10 mg/mL] (103, 142, 143)	Long term-effective in reducing lip swelling. It requires multiple injection sessions and local block anaesthesia. Adverse effects: acute pain and transient worsening of swelling	D
High volume triamcinolone acetonide [40mg/ml] (53, 106)	Effective in long-term reduction of oro-facial swelling. Requires one single 3-weekly course and no block anaesthesia. Adverse effects: mild discomfort, skin pigmentations.	
Systemic corticosteroids and immunosuppressants		
Prednisolone (57, 141)	Short-term courses effective in reducing facial swelling and oral ulcers. Side effects from chronic therapy: osteoporosis, diabetes, cataract, Cushing's syndrome.	D
Mycophenolate mofetil (109)	Long-term effectiveness in reducing orofacial swelling and ulceration. It requires monitoring of toxicity.	
Anti-TNF strategies		
Thalidomide (92,117,144)	Effective in the short-term management of OFG. Side effect: Neuropathy and teratogenesis.	D
Infliximab (117,145–148,119)	Short-term reduction in orofacial swelling and oral ulceration. It requires multiple infusions. Adverse effects: possible infusion reaction, infection, increased risk of cancer.	
Adalimumab (149)	Satisfactory results for oral ulceration. Adverse effects: possible infusion reaction, infection,	

	increased risk of cancer.	
Diet modification		
Cinnamon- and Benzoate free (88)	Improvement in swelling and inflammation. Compliance can be a limitation. Patch tests not predictive of response.	D
Avoid cross reacting food in patients with positive skin prick testing (45)	Failed to show significant improvement.	
Low phenolic acid diet (120)	Improvement in swelling and inflammation. The diet was nutritionally inadequate.	

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