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INVITED REVIEW
HOT TOPIC

Orofacial granulomatosis – a 20-year review

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Orofacial granulomatosis (OFG) is the presence of persistent enlargement of the soft tissues of the oral and maxillofacial region, characterized by non-caseating granulomatous inflammation in the absence of diagnosable systemic Crohn's disease (CD) or sarcoidosis. Over 20 years have passed since OFG was first described and an extensive review of the literature reveals that there is no consensus whether OFG is a distinct clinical disorder or an initial presentation of CD or sarcoidosis. Furthermore, the precise cause of OFG is still unknown although several theories have been suggested including infection, genetic predisposition and allergy. The clinical outcome of OFG patients continues to be unpredictable. Current therapies remain unsatisfactory. Regular clinical review is indicated to identify the development of gastrointestinal or systemic involvement. The aim of this review was to analyse the developments in our understanding of the aetiology, pathogenesis and treatment protocols, with particular emphasis on management and outcomes of OFG since this entity was first described in 1985.
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Introduction

Granulomatous lesions restricted to the oral cavity, the lips and perioral areas of the face may occur for a variety of reasons. A case describing facial palsy and orofacial oedema was reported by Melkersson (1928). Subsequently, the term Melkersson–Rosenthal syndrome (MRS) was proposed by Rosenthal to describe the triad of persistent lip or facial swelling, recurrent facial paralysis and fissured tongue (Rosenthal, 1932). A monosymptomatic variant of MRS – the presence of granulomas in the lip, presenting as marked lip swelling, was described by Meischer as cheilitis granulomatosa (Miescher, 1945). In addition, oral granulomas can occur in such systemic conditions as tuberculosis (TB) (Shengold and Sheingold, 1951) Crohn's disease (CD) (Crohn *et al*, 2000) and sarcoidosis (Wiesenfeld *et al*, 1985).

Wiesenfeld *et al* (1985) introduced the term orofacial granulomatosis (OFG) to describe the occurrence of granulomas in the orofacial region in the absence of any recognized systemic condition. Typically, OFG presents as recurring labial swellings that persist, resulting in enlargement of the lip(s). This can also be associated with oral ulceration, gingival overgrowth and a cobblestone appearance of the buccal mucosa. The labial swellings are characterized histologically by non-caseating epithelioid cell granulomas and lymphoedema. These histological features are indistinguishable from CD or systemic sarcoidosis. OFG encompasses the previously recognized MRS and cheilitis granulomatosa of Mieschke (Wiesenfeld *et al*, 1985; Challacombe, 1997).

The available literature shows the nomenclature of OFG lacks specificity. Recently, a question has been posed to determine whether OFG is a manifestation of a separate and specific inflammatory bowel disease (Sanderson *et al*, 2005). Furthermore, the aetiology and pathogenesis of OFG as a condition that is restricted to the orofacial region remain unclear. Several theories link OFG with food substances, food preservatives, dental materials and microbiological agents (Guttman-Yassky *et al*, 2003; Taibjee *et al*, 2004). The pathogenesis of OFG points towards a delayed hypersensitivity with inadequate data to suggest a firm genetic background. Furthermore, current treatment protocols are based on small case studies and rational therapy does not seem to be readily available (Rogers, 1996). The aim of this review was to analyse the developments in our understanding of the aetiology, pathogenesis and treatment protocols of OFG since the first description in 1985.

Methods

Literature retrieval was carried out using the computerized database 'PubMed Medline' using the main key

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words 'orofacial granulomatosis' (86 references), 'Melkersson–Rosenthal syndrome' (296 references and 30 duplicates of first search), 'cheilitis granulomatoses' (28 references, all duplicates), 'oral mucosa and Crohn's disease' (192 references, 16 duplicates),. The year of publication was not specified, non-English abstracts were excluded. Three articles were ignored as they were un-authored (e.g. news items) and three articles added prior to 1950, two of which were non-English (Melkersson, 1928; Rosenthal, 1932; Miescher, 1945). Articles were ignored prior to 1995 (116 references) other than those mentioned above. Further, only those case reports were included if they reported more than three patients or included unique aetiological agents or treatment protocols.

Clinical features

Orofacial granulomatosis is an uncommon but increasingly recognized disorder. The classic presentation is that of a non-tender recurrent labial swelling that may eventually become persistent (Wiesenfeld *et al*, 1985). Other oral manifestations include; angular cheilitis, mucosal ulcerations, vertical fissures of the lips, mucosal tags and lingua plicata. In addition, relapsing craniofacial neurological disorders, notably recurrent peripheral facial paralysis have been described. One study describes atypical onsets occurring in 48% of cases (Mignogna *et al*, 2003). As a consequence, swelling of the periorbital, zygomatic, chin and cheek areas should be carefully evaluated and appropriate history, examination and investigations undertaken to make an accurate diagnose and provide appropriate therapy.

Aetiology and pathogenesis

The aetiology of OFG has been a matter of debate since the term was first coined. There have been five processes that have been implicated in the causality of OFG; genetics; food allergy; allergy to dental materials; infective; and immunological. There are only a few reports providing limited data to support each of these postulated causes.

Genetic

The literature does not provide adequate data to support the contention that OFG has a genetic background. In a study of 42 patients with OFG and their 171 relatives lingua plicata were seen in 10 (23%) families of these patients and other features, such as recurrent mild unilateral peripheral palsy and facial swelling were seen in six of the 42 families (Meisel-Stosiek *et al*, 1990). However, more recently, it has been reported that 10% of the normal population can have lingua plicata (van der Waal *et al*, 2001) thus weakening the previous postulated link with a familial association. Further, an association between OFG and human leucocyte antigen (HLA) has been investigated and the two studies available do not show a strong link between HLA and pathogenesis of OFG (Satsangi *et al*, 1994; Gibson and Wray, 2000). The most recent of these studies reported the serological HLA typing of 16 patients with biopsy-proven OFG (Gibson and Wray, 2000) and found a significant increase in certain HLA alleles in the OFG patients compared to a group of 516 patients from the same region (Gibson and Wray, 2000). These authors suggested that an immunological mechanism may underlie the clinical presentation of OFG and that patients with specific HLA haplo-types may be more likely to suffer from OFG.

Food allergy

Various food substances and food additives have been purported to be either the cause or the precipitant event in OFG. Such antigenic irritants are thought to evoke a delayed type hypersensitivity and this general concept is supported by research showing that up to 60% of a group of 75 patients with OFG are atopic (James *et al*, 1986). This study questioned patients directly regarding a history of infantile eczema, hay fever or extrinsic asthma and quantitatively screened for specific IgE levels to common allergens using the radioallergosorbent test. Further, there have been nine case reports that implicate a variety of food stuffs that vary from dairy products (Levy *et al*, 1996), chocolates (Taibjee *et al*, 2004), carmosine (Sweatman *et al*, 1986), monosodium glutamate (Oliver *et al*, 1991), as well as alpha-lactobumin, toothpaste, eggs, peanuts, cinnamaldehyde, carbone piperitone and cocoa (Sciubba and Said-Al-Naief, 2003). A study of 48 patients with OFG who were patch tested for reaction to common food additives showed that 10 had a positive skin reaction and seven of these patients had improvement in their OFG with an elimination diet (Armstrong *et al*, 1997). Thus, at least in some patients, there would appear to be a role for allergy to food substances; however, the question remains whether these substances are the prime causative agents or just exacerbate the existing disease process.

Allergy to dental materials

Literature on the role of dental materials in OFG consists of three separate studies attempting to make this link. The first reported a patient with OFG purportedly associated with intra-oral cobalt (Pryce and King, 1990), the second described a 61-year-old female with intra-oral unilateral soft tissue swelling adjacent to an amalgam filling who also had a positive patch test for mercury (Guttman-Yassky *et al*, 2003). Following total amalgam replacement, the soft tissue swelling completely resolved (Guttman-Yassky *et al*, 2003). The final study outlines a patient with biopsy proven OFG and positive patch testing for mercury who refused total amalgam replacement and the symptoms were exacerbated (Lazarov *et al*, 2003). These latter authors attempt to link the continuation of the symptoms of OFG to the presence of amalgam dental material. All these three patients showed non-caseating granulomas on biopsy of the soft tissue swelling as well as a positive cutaneous patch test to dental filling material. However, the role of cutaneous patch testing in the diagnosis of OFG remains unclear. One recent study assessing the utility of cutaneous patch testing showed first that patients with OFG were more likely to have

reactions to food additives, especially benzoic acid and chocolate than other disease cohorts or controls (Wray *et al*, 2000). However, cutaneous patch test reactions to mercury and other metallic salts, indicating reactions to amalgam, were not observed in patients with OFG (Wray *et al*, 2000). Thus, there would appear to be no conclusive evidence to support a role for dental materials as the cause of OFG.

Infective

The implication of microbiological agents in the causation of OFG follows documentation of infective agents associated with chronic granulomatous conditions such as CD, sarcoidosis and TB. These studies have focused on *Mycobacterium tuberculosis*, *M. paratuberculosis*, *Saccharomyces cerevisiae* and *Borrelia burgdorferi*. One study from Turkey investigated the possible role of mycobacteria in six patients with biopsy proven OFG (Apaydin *et al*, 2004). Using molecular techniques, these investigators document the presence of *M. tuberculosis* complex in lip lesions of three out of six patients (Apaydin *et al*, 2004). Further, raised levels of serum antibody to mycobacterial 65 kDa stress protein were reported in seven of 10 OFG patients (Ivanyi *et al*, 1993). Finally, one group that was unable to detect M. paratuberculosis with polymerase chain reaction in 30 OFG patients (Riggio *et al*, 1997). It would thus seem that there is conflicting evidence of a role of Mycobacteria spp. in the aetiology of OFG.

An assessment of the presence of anti-*S. cerevisiae* antibodies in the serum showed that this is more common in patients with CD (63% IgG and 42% IgA) than in those with ulcerative colitis (15% IgG and 0% IgA) and healthy controls (8% IgG and 0% IgA) (Barnes *et al*, 1990). More recently, an assessment of the specificity of serum and salivary antibodies in patients with OFG with and without gut symptoms found that serum IgA anti-*S. cerevisiae* may be a highly specific serological marker for the development and progression of gut symptoms in patients with OFG (Savage *et al*, 2004). Further, these investigators found that non-specific saliva IgA levels were raised in patients with OFG, suggesting that salivary gland involvement specific for this disorder (Savage *et al*, 2004).

Finally, an investigation using both PCR and serological markers could not detect *Borrelia burgdorferi* in the serum of 12 patients with OFG (Muellegger *et al*, 2000). Thus, it would appear that there is insufficient evidence to support a definitive role for infections in the causation of OFG.

Immunological

Histologically, OFG is indistinguishable from CD and is characterized by non-caseating epithelioid granulomas with or without multinucleated giant cells. There is significant lymphoedema and both diffuse and focal aggregates of small lymphocytes (Wiesenfeld *et al*, 1985). The diversity of the cell surface markers present on lesional lymphocytes, as measured by T-cell receptor (TCR) diversity, has been shown to be no different from that of peripheral blood lymphocytes (Facchetti *et al*, 2000). This supports the hypothesis that OFG is a disease not driven by a single antigen, but rather a random influx of inflammatory cells. An assessment of the beta region of the variable portion of lesional TCR (TCR-V*B*) in a single patient with OFG showed that this variability was restricted suggesting a delayed hypersensitivity reaction rather than a super antigen (Lim *et al*, 1997). More recently, an immunohistochemical study of 10 patients with OFG assessed the inflammatory cell infiltrate for the expression of cytokines, chemokines and chemokine receptors (Freysdottir *et al*, 2007). These investigators provide evidence that the immune response in OFG patients is ThI and thus more cell-mediated immune response that has strong similarities with the inflammatory reaction present in gut lesions of patients with CD (Freysdottir *et al*, 2007). Clearly, these results reflect the immunological nature of both OFG and CD and hopefully further research will be able to clearly define sub-groups of patients who present with OFG alone or whose initial presentation of OFG is only the earliest manifestation of CD.

Diagnosis

The diagnosis of OFG is made by the clinical presentation of recurring orofacial swellings that persist leaving swellings that histologically consist of non-caseating granulomas. Other conditions that are also characterized by granulomatous formation are summarized in Table 1. CD, sarcoidosis and TB must be excluded by appropriate clinical and laboratory investigations. These tests include chest radiography (showing hilar adenopathy for patients with either TB and sarcoidosis); assessment of angiotensin – converting enzyme (increased in OFG and sarcoidosis); levels of folic acid, iron and vitamin B12 (decreased in CD); jejunal biopsy and endoscopy (abnormalities in CD); and tuberculin skin test (positive in TB).

Immunological measures have been reported to be able to distinguish between patients who have OFG, patients who have CD without oral involvement and patients who have both oral and gut CD (Savage *et al*, 2004). This previous study found that levels of salivary IgA was useful in discriminating between patients who have oral involvement, either those with OFG, or those patients who have oral manifestations of their CD and those patients who have only gut CD without any oral involvement (Savage *et al*, 2004). It is as yet unclear if such a test can be used predicatively.

More recently, capsule endoscopy has been proposed as a less invasive method of assessing the gut for the presence of abnormalities in patients with OFG and the efficacy of this method in comparison with endoscopy and barium X-ray for determining the presence and extent of CD in patients with OFG is currently under investigation (Ibrahim *et al*, 2007).

Management

Spontaneous remission of OFG is rare (Sciubba and Said-Al-Naief, 2003) and the treatment of symptomatic

Table 1 Granulomatosis disorders that may have clinical features similar to orofacial granulomatosis (OFG)

Disease	*Features different to OFG*
Crohn's disease	Patients most commonly have ileal (usually terminal) and/or rectal/oral disease. The orofacial features are identical to those of OFG, although orocutaneous fistulas may (rarely) occur in Crohn's disease
Sarcoidosis (usually chronic)	Chronic sarcoidosis may give rise to features similar to OFG. Affected patients may also have pulmonary, cutaneous, lachrymal, salivary neurological and/or skeletal features of sarcoidosis
Allergic angioedema	Manifests as non-pitting oedema of the lips, tongue, pharynx and face. Can be features of anaphylaxis. There are may be an identifiable precipitant and patients may have a history of atopic disease (allergic rhinitis, asthma, atopic eczema or drug allergies) Histology does not demonstrate Granulomatous inflammation
Mieschke's cheilitis (Schuermann's granulomatous cheilitis)	Manifests as labial enlargements and has histopathology of OFG
Melkersson–Rosenthal syndrome	Manifests as labial enlargement, fissuring of the tongue and lower motor neuron facial nerve palsy and has histopathology of OFG – a variant of OFG
Tuberculosis	Rarely affects the lips. Manifests as localized swelling and ulcers. Usually arises in immigrant groups and HIV-infected individuals. Usually contains caseating granulomas

patients continues to be unrewarding, especially if there is a delay in diagnosis. After recurrent attacks of regular intervals, the swelling becomes indurated (Ziem *et al*, 2000) and permanent, resulting in significant cosmetic concern and can interfere with speaking and eating (Mignogna *et al*, 2003). For reasons of the uncertainty of the aetiology of the disease, rational therapy is, as yet, not available (Rogers, 2000).

Elimination diets to identify and exclude dietary allergens have been advocated in a number of case studies (Patton *et al*, 1985; Sweatman *et al*, 1986; Reed *et al*, 1993; Armstrong *et al*, 1997). The data supporting the efficacy of these extensive, time consuming diets are limited and often very unrewarding for individual patients.

Corticosteroids have been shown to be effective in reducing facial swelling and preventing recurrences and are considered the mainstay of therapy. An interesting retrospective analysis of a group of patients allowed one group to postulate a gradation of treatments, depending on severity of lip swelling (van der Waal *et al*, 2002). Patients with mild swelling were commenced on topical steroids. More pronounced swelling of the lip or deterioration of lip swelling was treated with intralesional triamcinolone 0.1% injections, whereas patients with more extensive lip swelling were initially treated with systemic medication. Surgery was performed only in severely disfiguring cheilitis and once the disease had been brought into a quiescent phase (van der Waal *et al*, 2002). The criteria for choice of treatment would seem to be subjective with little scientific basis for selecting one treatment protocol over another. However, the escalation of treatment dependant upon clinical findings would appear clinically rational.

The use of intralesional corticosteroids has been shown to be effective in several further studies (Eisenbud *et al*, 1972; Krutchkoff and James, 1978; Allen *et al*, 1990) Multiple injections were often required and the pain of triamcinolone injections makes repeated therapy difficult, especially in children and may limit the volume of corticosteroid that can be injected. In an attempt to assess prospectively healing following intralesional triamcinolone injections Mignogna *et al* (2004) assessed five patients who received 2–3 injections over a 2- to 3-week period. The most well documented study attempting to undertake this treatment in a rational prospective reported the treatment of seven patients with OFG who had high-volume intralesional triamcinolone injections (Mignogna *et al*, 2004). Lip size in these seven patients was reported as either normal or cosmetically acceptable after a mean 19 month period (8–30 month) of follow-up. These investigators used a form of 'extended release' triamcinolone that may have enhanced their reported level of efficacy; nevertheless, if the patients can tolerate this repeated intra-lesionsal injections, then this is a reportedly good outcome (Mignogna *et al*, 2004).

Clofazimine has been reported to be effective in the management of OFG (Sussman *et al*, 1992; van der Waal *et al*, 2002). Clofazimine is a lipophilic dye that is thought to be a scavenger of hypochloric acid reducing the chlorination of proteins by neutrophils; however, the exact mechanism in OFG remains unknown. Although this agent has been reported to be effective in OFG, what is not clear is the exact protocol that these patients underwent, how often and for how long they were treated, what length of time these patients were followed up post-treatment and how remission was measured.

Low-dose thalidomide has been shown to be successful in treating five patients with clinical features of OFG recalcitrant to previous topical and systemic immunosuppressant therapy (Hegarty *et al*, 2003). However, because of its potentially teratogenic action, thalidomide cannot be prescribed to females of child-bearing age and needs to be closely monitored in those in whom it is used with 6-monthly sensory nerve action potentials. Nevertheless, in patients who have failed multiple treatments and whose disease continues to progress, low-dose thalidomide may be an option that requires consideration. Topical tacrolimus ointment has also been reported to be effective in the treatment of oral and perineal CD in children, with no evidence of significant systemic absorption (Casson *et al*, 2000).

Tumour necrosis factor alpha (TNF-α) has been postulated as having a central cytokine in the pathogenesis of CD and recently inflixamab, a chimeric monoclonal antibody directed against TNF-α, has been shown to be highly efficacious in patients with colitis associated with CD (Targan *et al*, 1997; Mahadevan and Sandborn, 2001; Targan *et al*, 1997; Mahadevan and Sandborn, 2001). Adalimumab, a recombinant monoclonal antibody that also binds to TNF-α receptors, has been shown with preliminary data to have similar efficacy to Inflixamab in CD patients; however, a recent case report of florid bilateral peri-oral cellulites occurring in a patient being treated with adalimumab for OFG indicates that clinical efficacy in the treatment of CD is not always readily translatable to OFG (Gaya *et al*, 2006).

Conclusion

Orofacial granulomatosis is an uncommon clinical disease. The available literature does not provide a clear understanding of the aetiology and the underlying pathological process. There is a marked diversity of aetiological agents documented by case studies ranging from food substances, dental materials and microbiological agents. Furthermore, a genetic predisposition is lacking. Delayed type hypersensitivity reactions appear to play a significant role, but the stimulating antigen varies from patient to patient. OFG treatment protocol is based on clinical management of various systemic granulomatous diseases and on limited case studies of patients with OFG. The advantage of an early diagnosis and limited use of systemic steroids on long-term patient outcome are highlighted in the literature. Although there are several treatment options emerging, such as anti-TNF-α antibodies, the mainstay of treatment for patients with OFG would appear to be individually tailored depending on a changing clinical presentation. Both clinician and patient need to be aware of the extremely frustrating nature of OFG and the common need to change treatment depending upon the changing severity of the disease process. An escalation through a number of topical medications with variable strength and efficacy, the occasional need for a course of intralesional injections and ultimately, the possibility of requiring long-term systemic medication, must be contemplated and openly discussed. Surgery should probably be performed only on patients with severely disfiguring cheilitis and preferably during a quiescent phase of the disease.

Author contributions

All authors contributed to the preparation of this article.

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