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ORIGINAL ARTICLE

Onset and progression of clinical manifestations of orofacial granulomatosis

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BACKGROUND: There remain few studies describing in detail the early occurrence and long-term progression of clinical manifestations of orofacial granulomatosis (OFG) in a substantial number of patients.
OBJECTIVES: The aim of this study was to determine the early and late clinical manifestations of a large case series of patients with OFG.
PATIENTS/METHODS: Clinically relevant data of 49 patients with OFG who attended an Oral Medicine unit in the UK were examined retrospectively. The analyzed parameters included occurrence and typology of initial manifestations at onset and with respect to long-term follow-up.
RESULTS: Five major patterns of disease onset were observed. Recurrent facial swelling with/without intra-oral manifestations was the single most common presentation at onset followed by intra-oral ulcers, and other intra-oral and neurological manifestations. The majority of patients later developed a spectrum of additional features.
CONCLUSIONS: OFG results in multiple manifestations at different time points. The disease onset is characterized by manifestations other than facial swelling in about half of affected individuals. However, patients can develop cosmetically unacceptable lip/facial swelling at a later stage. Nearly all affected individuals ultimately develop lip/facial swelling while about half of all patients develop oral ulceration.
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Keywords: orofacial granulomatosis; labial swelling; ulceration; granulomas; facial palsy

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Introduction

Orofacial granulomatosis (OFG) is a granulomatous disorder that typically affects the oro-facial region. It can cause recurrent or chronic persistent swelling of the orofacial tissues and oral mucosal ulceration together with a spectrum of other orofacial features (Leao *et al*, 2004) (Table 1). OFG is often characterized by the presence of granulomas in the sub-epithelial stroma (Hegarty *et al*, 2003).

The aetiopathogenesis of OFG is largely unknown. Current hypotheses have been recently reviewed in detail by Tilakaratne *et al* (2008). The clinical features of OFG are identical to oro-facial manifestations of Crohn's disease, although in contrast to the latter there is no consistent evidence of attendant inflammatory bowel disease. Similar to Crohn's disease, OFG shows several

Table 1 Clinical manifestations of orofacial granulomatosis

Intra-oral manifestations
Aphthous-like flat round-shaped ulceration
Linear ulceration (often with surrounding raised borders, affecting buccal and/or labial vestibules)
Cobblestoning
Gingival enlargement (granulomatous gingivitis)
Mucosal tags
Tongue fissuring
Tongue swelling
Extra-oral manifestations
Lip swelling
Periorbital swelling
Swelling of zygomatic and mental areas
Eyelid swelling
Median and angular cheilitis
Neurological manifestations
Lower motor neuron palsy of the facial nerve
Changes in taste, hearing, or earache
Palsy of glossopharyngeal nerve
Palsy of vagus nerve
Hyperidrosis
Glossodynia
Acroparesthesia
Lacrimation
Sweating
Migraine-like headache
Blepharospasm

similarities with other inflammatory and granulomatous disorders that can affect the head and neck area. Chronic oro-facial swelling, with or without ulceration and inflammation of intra-oral tissues can be found in sarcoidosis, some deep fungal infections, leprosy, tuberculosis, some acquired and hereditary forms of angioedema, foreign body and delayed-hypersensitivity reactions (Neville *et al*, 2002). OFG is believed to be aetiopathologically distinct from these disorders as their major distinctive clinical signs, symptoms and/or laboratory changes are typically lacking in OFG patients (Wiesenfeld *et al*, 1985). It is probable that OFG represents a spectrum of disease that ranges from localized granulomatous inflammation of the lips (granulomatous cheilitis, Miescher's cheilitis), through orofacial swelling with mucosal ulceration to disease with neurological deficit and lingual fissuring (Melkersson-Rosenthal Syndrome) (Mignogna *et al*, 2003; Sciubba and Said-Al-Naief, 2003; El Hakim and Chauvin, 2004; Kauzman *et al*, 2006).

Lip and in general oro-facial swelling is traditionally reported as the most frequent manifestation and common diagnostic feature of OFG (Alawi, 2005). Indeed it is the most common reason for which patients seek medical attention. However, some authors have suggested that the clinical features of OFG can be highly variable and dynamic, especially when early manifestations at disease onset are compared with long-term clinical features (Zimmer *et al*, 1992; Mignogna *et al*, 2003).

There remain however few reports of substantial numbers of patients attending a single centre to allow clear descriptions of the early and late clinical features. The aim of this study was to describe the clinical features of a large group of OFG patients attending a single clinical centre over a period of more than 20 years, and to focus on potential differences between manifestations at onset and during the course of the disease. This study did not include patients with Melkersson-Rosenthal syndrome, and patients with Crohn's disease and sarcoidosis (diagnosed either before or after the onset of oro-facial manifestations) were excluded, hence the present patients represent the largest homogenous group of individuals with OFG reported in the past two decades.

Subjects and method

The study group comprised 49 individuals with OFG who attended the Oral Medicine Unit of UCL Eastman Dental Institute and UCLH Eastman Dental Hospital between 1985 and 2008. Diagnostic criteria included: (i) presence of clinical features belonging to the spectrum of OFG, (ii) histopathological evidence of non-caseating granulomas and (iii) exclusion of other granulomatous disease on the basis of clinical, histopathological and laboratory investigations (Mignogna *et al*, 2003; Leao *et al*, 2004). All patients met at least criteria (i) and (iii). Patients who developed intestinal inflammation of Crohn's disease after the onset of orofacial manifestations were re-categorized as having oral Crohn's disease and were thus excluded from the study.

Data regarding patients' demographics, past medical history, diagnostic features, treatment modalities, short- and long-term outcome, adverse side effects of therapy, and monitoring investigations were systematically extracted from the case file of each patient and are reported in detail elsewhere (K Al Johani, DR Moles, SR Porter, S Fedele, unpublished data). Disease onset was evaluated on the basis of patients' history, referral letter and/or first clinical examination at the Oral Medicine clinic. Long-term clinical manifestations occurring during the course of the disease were evaluated on the basis of clinicians' descriptions in the clinical notes and photographs taken during clinical reviews until January 2008. The impact of therapies on the behavior of clinical manifestations was not considered. The review of clinical notes and comparisons between early and late clinical features were performed independently by two authors (K.A. and S.F.).

Results

The group comprised 27 males (55.0%) and 22 females (45.0%). The mean age at the time of clinical diagnosis by Oral Medicine specialists was 32.4 years (range: 7.4–72.1 years). Considering that the mean reported duration of oral signs/symptoms before definitive diagnosis was 44 months (range: 4–192 months), the mean age of patients at disease onset was estimated to be 28.7 years. The observation period of this cohort of OFG patients varied from 1 to 15 years (mean 2.9, median 1.8).

Clinical features at disease onset

Analysis of data indicated that there were five major patterns of disease onset. These comprised: facial swelling only (group 1), facial swelling with other manifestations (group 2), oral ulceration only (group 3), other intra-oral manifestations without facial swelling (e.g. gingival hyperplasia) (group 4) and neurological manifestations only (e.g. facial palsy) (group 5) (see Table 2 and Figure 1). The most commonly reported abnormality at disease onset was recurrent oro-facial swelling, reported by 26 (53.1%) patients (groups 1 and 2). Twenty-five patients (51.0%) had swelling of one or both lips, and one patient (2.1%) reported bilateral malar swelling. Fifteen (group 1) of these 26 patients reported oro-facial swelling to be their only initial manifestation (upper and/or lower lip in 14 and malar area in one) while in the other 11 patients (group 2) the swelling of the lips co-existed with other extra- and/or intra-oral manifestations including angular cheilitis (one patient), perioral erythema (one), fissuring plus angular cheilitis plus mucosal cobblestoning and tags (one), swelling of the cheek (one), mucosal cobblestoning and gingival enlargement (one), intra-oral ulceration (four), gingival enlargement (one) and lip fissuring (one). Lymph node swelling was never found to be the only presenting manifestation of OFG.

Intra-oral ulcers as the only presenting sign were reported by 14 patients (28.6%) (group 3) consisting of

Table 2 Clinical features of the 49 patients with orofacial granulomatosis at disease onset and during long-term follow-up

Patients	*Manifestation at disease onset*	*Subsequent manifestations*
Group 1		
1	Upper/lower lip swelling	Intra-oral ulceration, cobblestoning, cervical lymphadenopathy.
2	Upper/lower lip swelling	Intra-oral ulceration and cobblestoning.
3	Right cheek swelling	Upper/lower lip swelling
4	Upper lip swelling	Lower lip swelling, cobblestoning and tags
5	Upper lip swelling	Intra-oral ulceration and cobblestoning
6	Upper lip swelling	None
7	Lower lip swelling	Intra-oral ulceration
8	Lower lip swelling	Upper lip swelling, intra-oral ulceration
9	Lower lip swelling	Perioral erythema
10	Lower lip swelling	Upper lip swelling
11	Lower lip swelling	Cervical lymph node swelling
12	Lower lip swelling	None
13	Lower lip swelling	None
14	Lower lip swelling	None
15	Lower lip swelling	None
Group 2		
16	Upper/lower lip swelling and perioral erythema	Intra-oral erythema, mucosal tags and cobblestoning., hypertrophy of palatal mucosa, cervical lymphadenopathy
17	Upper/lower lip swelling, cobblestoning and gingival hyperplasia	Upper/lower lip swelling
18	Upper lip swelling and intra-oral ulceration	Lower lip swelling, cobblestoning., cervical lymph node swelling
19	Upper/lower lip swelling and fissuring	Perioral erythema, cobblestoning.
20	Lower lip swelling and intra-oral ulceration	Gingival hyperplasia
21	Upper lip swelling and angular cheilitis	Lower lip swelling
22	Upper/lower lip swelling and fissuring, angular cheilitis, tags and cobblestoning	Gingival hyperplasia, perioral erythema
23	Upper lip swelling and gingival hyperplasia	Cheek swelling
24	Lower lip swelling and intra-oral ulceration	None
25	Lower lip swelling and intra-oral ulceration	None
26	Upper/lower lip and cheek swelling	None
Group 3		
27	Intra-oral ulceration	Upper/lower lip swelling
28	Intra-oral ulceration	Upper/lower lip and cheek swelling, cobblestoning
29	Intra-oral ulceration	Lower lip swelling
30	Intra-oral ulceration	Upper/lower lip swelling, angular cheilitis
31	Intra-oral ulceration	Lower lip swelling, cobblestoning, tags, cervical lymphadenopathy
32	Intra-oral ulceration	Cobblestoning
33	Intra-oral ulceration	Lower lip and cheek swelling, tags, and cobblestoning.
34	Intra-oral ulceration	Lower lip swelling, cervical lymph node swelling
35	Intra-oral ulceration	Upper/lower lip swelling, lip abscess and mucosal tags
36	Intra-oral ulceration	Lower lip swelling, perioral erythema, cobblestoning, tags, cervical lymph node swelling
37	Intra-oral ulceration	Upper lip swelling
38	Intra-oral ulceration	Lower lip swelling
39	Intra-oral ulceration	Lower lip and cheek swelling, cobblestoning
40	Intra-oral ulceration	Upper lip and cheek swelling, angular cheilitis, cobblestoning, cervical lymph node swelling
Group 4		
41	Tongue swelling	Gingival hyperplasia
42	Gingival hyperplasia	Upper/lower lip swelling and cobblestoning
43	Gingival hyperplasia	Upper lip swelling, cobblestoning
44	Gingival hyperplasia and cobblestoning	Lower lip swelling
45	Cervical lymph node swelling and gingival hyperplasia	Intra-oral erythema and mucosal tags
Group 5		
46	Facial palsy	Upper lip and cheeks swelling, perioral erythema
47	Facial palsy	Upper/lower lip swelling, cobblestoning
48	Chronic paroxysmal hemicrania	Upper/lower lip swelling
49	Facial palsy	Lower lip swelling, gingival hyperplasia, cobblestoning and tags

either superficial aphthous-like ulcers or linear, deep ulcers of the vestibular fold areas.

With regard to other intra-oral manifestations (group 4), gingival enlargement was the presenting sign of OFG in four patients (8.2%), one of whom also had cobblestoning while the other had cervical lymph node swelling. One patient (2.1%) reported swelling of the tongue as the probable initial feature of OFG. Mucosal tags and/

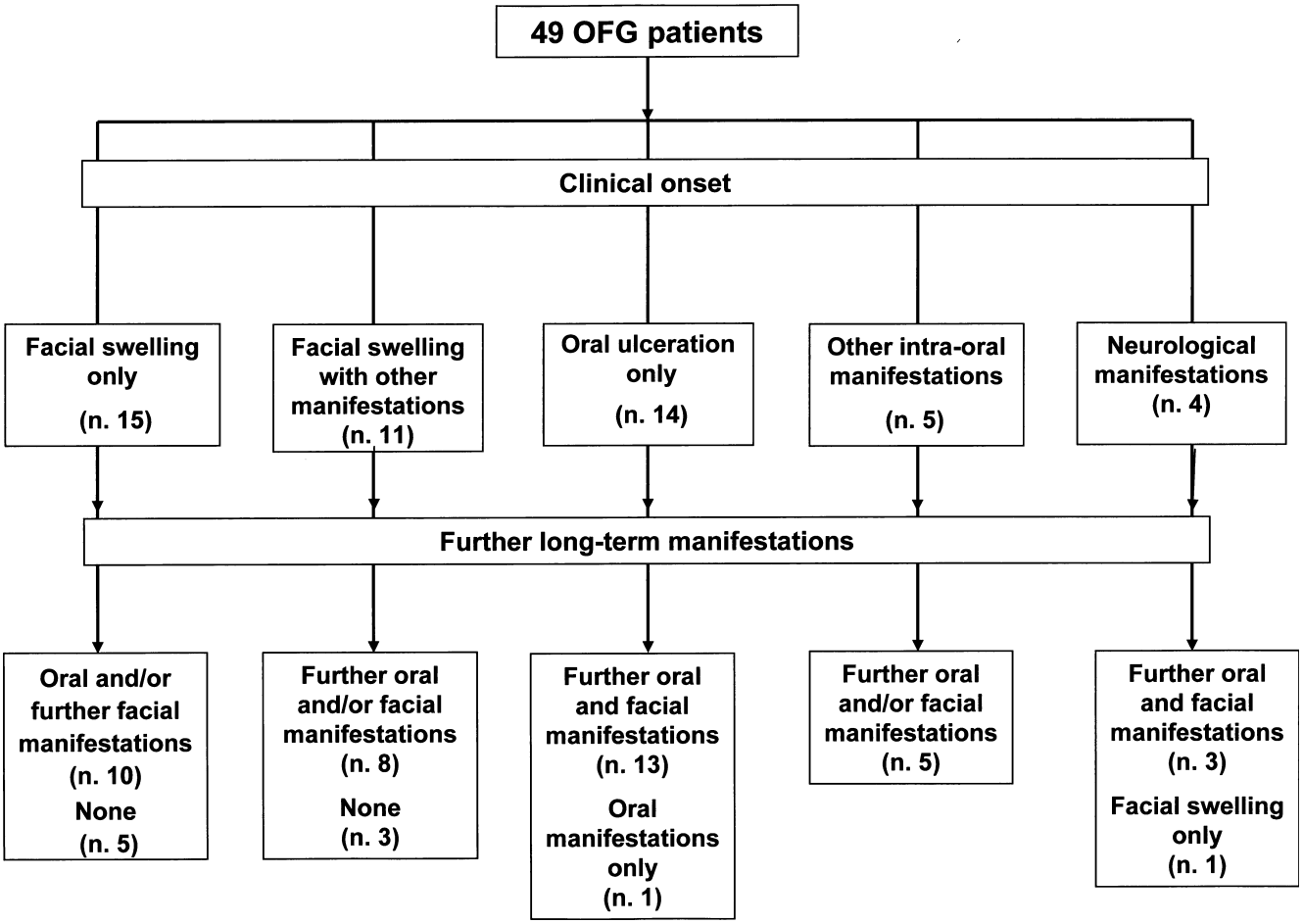

Figure 1 Patterns of disease onset and long-term manifestations in this cohort of 49 patients

or cobblestoning were never found to be the only presenting sign of OFG.

One or more episodes of facial nerve palsy, at disease onset, were reported by three patients (6.1%) and one (2.1%) patient had chronic paroxysmal hemicrania as presenting manifestation of OFG (group 5).

Long-term clinical features

The majority of patients (42/49; 85.7%) developed a variety of different additional features of OFG following its initial manifestation (Table 2 and Figure 1). Ten out of the 15 patients (66.7%) with OFG who initially presented with facial swelling only (group 1) developed other manifestations during the course of the disease including intra-oral ulceration only (one patient), intra-oral ulceration and cobblestoning (two), labial swelling (two), labial swelling and ulceration (one), labial swelling with cobblestoning and tags (one), perioral erythema (one), cervical lymph node swelling (one) and cervical lymphadenopathy with cobblestoning and mucosal ulceration (one).

Eight of the 11 patients (72.7%) who initially had facial swelling co-existing with other clinical features (group 2) developed further signs of OFG including labial and buccal swelling (three patients), labial swelling with cobblestoning and cervical lymphadenopathy (one), intra-oral erythema, tags and cobblestoning, hyperplasia of palatal mucosa and cervical lymph node swelling (one), perioral erythema plus gingival hyperplasia or cobblestoning (two) and gingival enlargement only (one).

Thirteen of the 14 (92.9%) patients who had only intra-oral ulceration at disease onset (group 3) eventually developed facial swelling only (four patients), or swelling associated with cobblestoning (three), angular cheilitis (one), lymph node swelling with or without tags (two), cobblestoning with tags (one), tags with perioral erythema and lymphadenopathy (one) or with angular cheilitis and lymphadenopathy, labial abscess and tags (one). In only one patient intra-oral ulceration was followed by cobblestoning without any labial/facial swelling.

Within group 4, the patient with tongue swelling at disease onset eventually developed gingival enlargement. The patients presenting with gingival enlargement at disease onset without facial swelling (4/49) developed intra-oral erythema and tags (one patient), or labial swelling (one) and labial swelling plus cobblestoning (two) (group 4).

All four patients with neurological manifestations only at disease onset (group 5) later developed labial swelling alone (one patient), labial swelling plus mucosal

cobblestoning (one), labial swelling with gingival hyperplasia, cobblestoning and tags (one) and labial and buccal swelling plus perioral erythema (one).

Twenty of the 23 (87%) patients who had intra-oral (groups 3 and 4) or neurological (group 5) manifestations only at disease onset (individuals presenting without facial swelling) had swelling of one or more facial areas during the following years of clinical monitoring. Similarly, among those patients who only had facial swelling at disease onset (15), the majority (10/15; 66.7%) eventually developed intra-oral manifestations.

In total, 47 of the 49 patients (95.9%) developed facial swelling along the course of their disease whilst mucosal ulceration occurred only in 24 (49%). The lips were affected in 46 of the 47 patients with facial swelling (98%). Labial enlargement affected both lips in 20 patients (43.4%), the lower lip only in 19 (41.3%) cases and the upper lip in 7 (15.2%) patients. Full-blown symptomatic OFG (intra-oral ulceration and facial swelling) occurred in 23 patients (46.9%) during the disease course.

Discussion

Orofacial granulomatosis is a chronic inflammatory disease with the potential to adversely affect the quality of life of patients by virtue of persistent labial and/or facial swelling, painful oral ulcerations and occasionally neurological manifestations (Somech *et al*, 2001). There are no detailed studies of the clinical onset and long-term behavior of this disorder. The present study attempted to clarify these issues by virtue of a retrospective analysis of a group of patients with OFG who were managed at a single centre for more than 20 years. The study represents the largest homogenous group of individuals diagnosed solely with OFG reported in the past two decades. As the majority of previous clinical studies of OFG-like diseases included patients with Crohn's disease and those with hypersensitivity reactions, their findings should be interpreted with caution as these disorders may present and behave differently from OFG (Patton *et al*, 1985; Wiesenfeld *et al*, 1985; James and Ferguson, 1986; Williams *et al*, 1991). Labial swelling is traditionally indicated as the most common clinical feature of OFG. It is also reported as being the most frequent manifestation at disease presentation (Alawi, 2005). However, few authors have reported that clinicians should not focus solely on labial swelling as patients with OFG can in fact present with multiple, temporary and multi-focal clinical features affecting intra-oral mucosa, gingivae, facial tissues and the craniofacial nervous system (Wiesenfeld *et al*, 1985; Mignogna *et al*, 2003). Moreover, different clinical manifestations have been reported to develop at different time points during the course of the disease (Zimmer *et al*, 1992; Mignogna *et al*, 2003). Mignogna *et al* (2003) reported that about half of their 19 OFG patients (9/19) had a disease onset characterized by the absence of labial swelling and occurrence of facial palsy, intra-oral manifestations and swelling of facial areas other than the lips. Seven of these nine patients eventually developed labial swelling. 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% (Zimmer *et al*, 1992). In partial agreement with these findings, the present study identified five patterns of disease onset (Figure 1) with facial swelling (53.1%) and oral ulceration (28.6%) being the most common initial manifestations. Most patients (85.7%) developed further facial and/or intra-oral manifestations over the years. This confirms the concept that the clinical behavior of OFG is multiform, progressive and highly variable, and that perhaps each patient's disease has a unique pattern of duration and presentation (Mignogna *et al*, 2003). Neurological manifestations are reported to affect between 8.3% and 57.1% of OFG patients (Wiesenfeld *et al*, 1985; Armstrong *et al*, 1997; Mignogna *et al*, 2003; Kanerva *et al*, 2008) and were observed in four patients of our cohort (8.2%). They all occurred at the onset of disease and never as subsequent clinical manifestation, suggesting that patients who do not present neurological involvement at an early stage of their disease are unlikely to develop it afterwards. Details of treatment are not reported in the present study. Nevertheless, it is unlikely that treatment has had any influence on the pattern of occurrence of clinical manifestations as: (i) the patients were homogeneously managed by the same group of clinicians and (ii) subsequent clinical features developed both before and after the start of therapy.

Conclusion

Little is known about clinical onset and early manifestations of OFG. The few data available suggest that early OFG can cause clinical manifestations other than labial swelling that can include transient facial palsy, mucosal ulceration, swelling of other areas of the face, and gingival hyperplasia (Rozen, 2001; Mignogna *et al*, 2003). The results of this study indicate the onset of OFG can be characterized by labial swelling in only half of the patients while in the other half early disease can cause intra-oral or neurological manifestations only. The long-term behavior of OFG can be subsequently characterized by the development of further clinical manifestations. It can be expected that most patients (up to 95.9% in the present study) develop during the course of the disease orofacial swelling and, less frequently (49%), intra-oral ulceration. Clinicians should consider the variable, progressive and multiform nature of OFG when they attempt early diagnosis and long-term management.

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Author contributions

K Al Johani and DR Moles designed the study, analysed the data and prepared manuscript. T. Hodgson assisted in the collection of data. SR Porter performed the plan of study and manuscript preparation. S Fedele performed plan of study, data analysis and manuscript preparation.

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