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REVIEW ARTICLE

Oral Crohn's disease: Is it a separable disease from orofacial granulomatosis? A review

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Abstract

Symptomatic oral Crohn's disease is comparatively rare. The relationship between orofacial granulomatosis, (where there is granulomatous inflammation and ulceration of the mouth in the absence of gastrointestinal disease) and true oral Crohn's disease is discussed along with the plethora of clinical oral disease presentations associated with both disorders and the differential diagnosis of oral ulceration in patients presenting to a gastroenterological clinic. Specific oral syndromes are outlined including the association between oral manifestations in Crohn's disease and the pattern of intestinal disease and their relationship to other recorded extraintestinal manifestations. The histological and immunological features of oral biopsies are considered as well as the principles of management of symptomatic oral disease. At present, it is suggested that both orofacial granulomatosis and oral Crohn's disease appear to be distinct clinical disorders.

Contents

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1. Introduction

Traditional teaching states that Crohn's disease is a disorder affecting 'the mouth to the anus,' however, isolated Crohn's disease of the upper gastrointestinal tract and especially oral Crohn's disease (OCD) is a relatively uncommon finding where understanding of its pathogenesis is evolving. In patients with Crohn's disease who present with oral ulceration, before a diagnosis of OCD is made, granulomas evident in biopsy material need to be differentiated from other granulomatous oral disorders including foreign-body reactions, sarcoidosis, typical and atypical mycobacterial infection and fungal sepsis.[1–3] The term orofacial granulomatosis (OFG) was coined by Wiesenfield et al. in 1995 to define the presence of granulomatous oral ulceration without intestinal involvement,[4] although it is recognized that granulomatous mouth ulcers may predate intestinal involvement in Crohn's disease.[5,6] The association between OFG and OCD currently remains unclear where the risk factors for the progression of OFG to 'full-blown' Crohn's disease are poorly understood. In some cases, diagnostic confusion may occur where there is an indeterminate colitis associated with aphthous oral ulceration; a generally more common finding in patients with ulcerative colitis.[7] This article outlines the clinical evaluation of the oral cavity, the pattern of oral lesions in patients with known Crohn's disease and their known association with other extraintestinal manifestations, discussing its clinical differentiation from patients with OFG. The current views concerning the pathogenesis of both conditions is discussed along with available data linking oral ulceration to the likelihood of the development of intestinal Crohn's disease. The difficulties in interpretation of the incidence of oral lesions in Crohn's disease are analyzed with a discussion of the management of symptomatic oral disease in OCD and OFG patients.

1.1. Clinical differentiation of oral Crohn's disease (OCD) and orofacial granulomatosis (OFG)

There is a plethora of oral manifestations which have been described in patients with Crohn's disease (Table 1). Many oral lesions described in Crohn's disease are somewhat non-specific, mimicking various forms of nutritional glossitis.[8–10] The range of lesions in Crohn's disease includes diffuse lip and buccal mucosal swelling, oral cobblestoning, buccal sulcus ulceration and mucosal tags.[11,12] Cobblestoning is usually located on the posterior buccal mucosa and may be associated with succulent mucosal folds with an intact epithelium whereas mucosal tags are more commonly found in the labial and buccal vestibules as well as in the retromolar region. Many of these lesions may be preceded by painless gingival enlargement[13] and this finding in its earliest stages should be distinguished from other known drug-related, systemic and idiopathic causes of gingival hypertrophy.[14] These latter non-specific lesions, (unrelated to OCD), show extensive deposition of collagen in the lamina propria with over-expression on immunohistochemistry within the pro-inflmmatory cellular infiltrates of matrix metalloproteinases, most notably MMP-3 and TIMP-2,[14] distinguishing them from true OCD or OFG, both of which are unassociated with these immunohistochemical changes. Ancillary oral lesions in OCD include angular cheilitis, scaly perioral erythematous rashes and frank intraoral abscess formation, although the latter presentation is comparatively rare.[15] Studies have also shown in patients with inflammatory bowel disease, that there is a higher prevalence of periodontal disease and caries than noted in the normal population, where as many as 60% of patients with Crohn's disease referred to dental units for assessment show evidence of cheilitis, labial and tongue fissuring, glossitis and aphthous stomatitis.[16,17] Depending on the clinical correlations and dedication towards oral diagnosis in patients with Crohn's disease, oral lesions may be identified in up to 60% of patients where in 5–10% of cases they may be the first manifestation of disease.[18]

By contrast, OFG may present with discrete ulcers although more commonly with lip and facial swelling as well as distinct conditions including pyostomatitis vegetans and the Melkersson–Rosenthal syndrome. The former condition manifests with soft pustular hyperplastic mucosal folds[19] although this has been reported uncommonly in ulcerative colitis and very rarely in childhood Crohn's disease.[20] The histology in this condition is fairly specific with localized eosinophilic infiltration within microabscesses associated with pseudoepitheliomatous hyperplasia and cellular acanthosis. These changes do not show IgA, IgG or complement deposition, distinguishing it from pemphigus vulgaris.[21] The Melkersson–Rosenthal syndrome which is a

Table 1 Oral manifestations/pathologies associated with Crohn's disease and orofacial granulomatosis.

Oral Crohn's Disease (OCD)	Orofacial granulomatosis (OFG)
Periodontal disease and caries	Lip swelling [a]
Aphthae/apthous stomatitis	Facial swelling
Diffuse lip and buccal mucosal swelling	Pyostomatitis vegetans
Oral cobblestoning	Melkersson–Rosenthal syndrome
Buccal sulcus ulceration	Frank ulcers (buccal with raised edges, aphthae, microabscesses)
Mucosal tags	
Cheilitis	
Labial and tongue fissuring	
Glossitis	
Palatal ulceration (rare)	

[a] Disease confined to the lips is referred to as Meischer's cheilitis granulomatosa.

rare presentation of OFG, comprises the triad of orofacial swelling, facial paralysis and a fissured tongue, (so-called *lingua plicata*) with lingual lesions most commonly located on the lateral aspect of the dorsum of the tongue.[22,23] In this condition, facial palsy develops slowly only after other clinical manifestations of OFG have already appeared. *Formes fruste* of this disorder may include patients who present only with isolated cheilitis (referred to as cheilitis granulomatosa of Meischer)[24] which is usually associated with extensive orofacial swelling spreading to the chin, nose and eyelids[25,26] and which may be responsive to Infliximab infusions in the absence of demonstrable gastrointestinal disease.[24,27]

Currently, OCD and OFG are separated on clinical grounds, where OFG tends to present with more labial pathology and less oral ulceration. Labial enlargement affects the upper and/or lower lips and is often persistent in nature rather than recurrent where the labial mucosa is granular and erythematous in appearance but where associated periroral midline and angular stomatitis tends to be more scaly and exfoliative. If ulceration is present in patients with OFG it takes one of 3 forms, including frank deep buccal ulcers with raised peri-ulcerative mucosa, aphthous-type ulcers or microabscesses which are usually located on the gingival margin or on the soft palate.

1.2. Histology of oral biopsies in OCD and OFG

The presence of granulomas on biopsy is the histological hallmark of both OCD and OFG, where the differentiation from other granulomatous oral disease is made on the clinical picture accompanying the oral disease.[3] Table 2 shows the differential diagnoses, diagnostic criteria and

Table 2 Differential diagnosis in the clinic of granulomatous and non-granulomatous oral ulceration detected in the gastrointestinal clinic.

Diagnosis	Extraoral findings	Additional diagnostic criteria
Granulomatous disorders		
Oral Crohn's disease (OCD)	Abdominal pain, diarrhea, rectal bleeding	Gastroscopy, colonoscopy
Orofacial granulomatosis (OFG)	NIL	
Foreign-body granuloma	NIL/fever	\
Sarcoidosis	Cough, fever, weight loss, erythema nodosum	Chest X ray, serum ACE,IL-2r
Oral tuberculosis	Cough, haemoptysis, fever	Z-N staining, Manotux, CD4 count, bronchoscopy
Deep mycotic ulcer	*Candidiasis*, *Histoplasmosis* *Paracoccidioidomycosis*, *Cryptococcosis*	Culture, CD4 count bronchoscopy
T cell lymphoma	Fever, weight loss, lymphaednopathy	T cell typing
Wegener's granulomatosis	Pulmonary, renal involvement ANCA antibodies	
Oral syphilis	Rash, genital ulceration	Treponemal antibody testing (FTA, TPHA)
Cat-Scratch Disease	Lymphaednopathy	Lymph node biopsy, anti-*Bartonella henselae* antibodies
ACE Angiotensin converting enzyme, IL-2 Interleukin-2, FTA Fluorescent Treponemal antibody, TPHA Treponeme Haemagglutination assay; ANCA Anti-neutrophil cytoplasmic antibodies		
Non-granulomatous disorders		
Recurrent aphthous stomatitis		
Nutritional deficiency		
Oral malignancy		
Coeliac disease	Nausea, bloating, anemia, dermatitis Herpetiformis	Duodenoscopy Serum antibody testing ϕ
Behçet's syndrome	Recurrent genital ulceration, uveitis, arthritis	Pathergy testing
Geographic tongue (benign migratory glossitis)		
HIV AIDS-related infection	Weight loss, fever, lymphadenopathy, KS lesions	HIV ELISA, viral load assay, CD4 count
Viral infection (Coxsackie, CMV, EBV, HSV 1/2)		Anti-viral ELISA
Sweet's syndrome [a]	Fever, leukocytosis, skin papules	Associated AML
Vasculitis		
Lichen planus		
Pemphigus		

CMV Cytomegalovirus, EBV Epstein–Barr virus, HSV Herpes simplex virus.
ϕ Anti-transglutaminase and anti-endomysial antibodies.
KS Kaposi's sarcoma.
ELISA Enzyme linked immunosorbent assay.
[a] Fever, neutrophilia, recurrent oral ulceration associated with acute myeloid leukemia (AML).

the specific testing required (where appropriate) in patients presenting with biopsy-proven oral granulomatous diseases as well as those presenting to the gastrointestinal clinic with persistent non-granulomatous oral ulceration. The commonest cause of oral granulomas is a foreign-body reaction usually as a response to a range of dental materials including retained impressions and amalgams as well as endodontic sealers[28] where this type of reaction more commonly presents as a mass rather than frank ulceration and is accompanied by typical foreign-body type giant cells surrounding foreign material on biopsy. Specific infectious conditions leading to granulomas include tuberculosis which is more often seen as deep ulcerative oral disease particularly in immunosuppressed patients where Ziehl–Neelsen staining shows typical acid-fast bacilli and where granulomas are caseating with an accumulation of Langhans-type giant cells.[29] Rarely fungal infections may be detected particularly occurring in Histoplasmosis, Cryptococcosis and Pacoccidiodomycosis.[30,31] Oral sarcoidosis is comparatively rare, usually being associated with systemic symptoms (fever, arthralgia, generalized lymphadenopathy and weight loss) as well as hilar lymphadenopathy and where the oral manifestations are typically multinodular with associated salivary gland enlargement.[32] Differentiation can be made by labial gland biopsy[33] and by serum angiotensin converting enzyme, IL-2receptor and IL-8 levels each of which correlates with disease activity.[34]

In OCD, there is a high reported rate of granulomata (between 75 and 100%) found in oral biopsies of discrete lesions, regardless of their form of presentation,[12,18,35–37] although there is a spectrum between the presence of discrete non-caseating granulomas through confluent granulomatous sheets of macrophages and multi-nucleate giant cells to loose granulomatous macrophage clusters. This may be accompanied by granulomatous lymphangitis and very commonly by marked fibrosis. In biopsy material, differential lymphocyte accumulation discriminates between OCD and OFG. In OCD, Th1 CD4+ lymphocytes are a hallmark[37,38] with an association with NOD2/CARD 15 mutational dysregulation on chromosome 16, particularly in those with associated ileal disease.[39,40] Mutations in this gene predispose towards granuloma formation possibly as a result of alterations in the innate immune response to bacterial flora where CARD 15 encodes for intracellular receptors for bacterial translocation.[39] This genetic finding has been linked to the detection of serum IgA antibodies to *Saccharomyces cerevisiae* in patients who have OCD as a further distinguishing factor separating it from cases of OFG.[41]

In OFG there is a postulated overstimulation of the Th2 CD4+ leucocyte pathway with evidence of a locally restricted T-cell receptor gene expression in the infiltrating lymphocytes derived from biopsies of lesions when compared with those obtained from normal oral mucosa. This is suggestive of a specific antigen-driven T cell clonal expansion[42,43] although the nature of the antigenic challenge in these patients has yet to be identified. This is coupled with a greater trend in patients with OFG to have coincident atopic disorders as part of a Th2 CD4+ overstimulation where a range of food hypersensitivities have been identified (particularly to cinnamaldehyde and benzoate additives).[44] Currently, there is no available evidence that standard or urticarial skin patch testing for patients with this type of OFG presentation is, however, beneficial.[45,46] Table 3 shows the histopathologic differences between OCD and OFG when a granulomatous oral biopsy is obtained.

1.3. Intestinal patterns of Crohn's disease presenting with oral pathology

There is no clear or expected pattern of gastrointestinal Crohn's disease presenting with oral manifestations.[47] Whereas it would be anticipated that upper gastrointestinal disease should be more common in such patients, there is little prospective data to support this view.[36,47] In this respect, Dupuy et al. have reported a greater male predominance, a young age of onset and a higher prevalence of upper gastrointestinal involvement in patients who present with oral manifestations in Crohn's disease where patients tend to have a more protracted clinical course.[48] Equally, Harty and colleagues have noted a higher incidence of concomitant perianal Crohn's disease in those patients also presenting with oral disease although their series numbers were small.[36] The natural history of oral disease associated with active Crohn's disease is presently somewhat unclear, where up to one-third of patients will continue to harbor oral manifestations during follow-up.[49] There is no significant difference regarding intestinal location or disease activity between patient subgroups which either cease or which continue to harbor OCD, implying a diagnostic advantage in oral examination only at the time of initial presentation. Children who harbor oral disease generally display a more significant disease burden, (a more severe Crohn's phenotype), corroborating the finding of the European Collaborative Study on Inflammatory Bowel Disease that the presence of upper gastrointestinal disease is a predictor of more severe disease activity overall.[50]

There is considerable debate concerning whether oral disease in patients with intestinal Crohn's disease should be considered as an extraintestinal manifestation or whether it is a reflection of overall mucosal disease activity. Despite the fact that oral disease may predate intestinal involvement,[5,6,51] it is often not included as a specific extraintestinal manifestations of Crohn's disease, where Monsén et al. in a Swedish epidemiology study excluded arthralgia, stomatitis and episcleritis in their clinical listing of extraintestinal manifestations.[52] Notably, aphthous stomatitis has some degree of clinical linkage with peripheral arthritis, ankylosing spondylitis, uveitis and erythema nodosum.[53] The

Table 3 Histopathologic and histomorphologic differences between OCD and OFG.

Pathologic features	OCD	OFG
Non-caseating granulomas	+	+
Loose macrophage clusters	+	–
Granulomatous lymphangitis	+	–
Fibrosis	+	+/–
Th-cell predominance	Th1	Th2
T cell clonality within lesions	–	+
IgA antibodies to *Saccharomyces cerivisiae*	+	–

accurate determination of extraintestinal manifestations in inflammatory bowel disease is a complex issue where if major extraintestinal disorders are counted, the prevalence is as high as 20–25%,[54] however, if all potential systemic effects and complications of therapy are included, almost all patients will be listed as having some form of an extra-intestinal manifestation. Whereas previously it has been reported that extraintestinal manifestations are commoner in those patients presenting with colonic Crohn's disease,[55] the intestinal location and pattern of Crohn's disease has not been found to be a significant factor on logistic regression for any specific extraintestinal presentation.[56] Moreover, in the pediatric population, it is suggested that the incidence of extraintestinal manifestations is significantly under-reported, where aphthous stomatitis (which occurs overall in about 8% of patients with inflammatory bowel disease), is about 3 times more common in patients with Crohn's disease than it is in ulcerative colitis.

The appearance of other non-oral extraintestinal manifestations shows a stronger association with disease activity at the time of diagnosis in both Crohn's and ulcerative colitis, suggestive of a common pathogenetic pathway between the development of the extraintestinal and the inflammatory intestinal disease[57,58] where the appearance of one extraintestinal manifestation increases the risk of development of another. Multiple extraintestinal manifestations are, however, uncommon occurring in only 4.5% of cases and are more common in patients with Crohn's disease.[53] Difficulties with interpretation of this data include the under-diagnosis of relevant associated extra-intestinal manifestations in some cases, the variability in the utilization of the term and the assessment of patient cohorts in cross-sectional studies where only a few patients will suffer from specific extraintestinal disorders at any one time. Variability in their reported incidence also reflects differences between prospectively and retrospectively collected series,[55] geographic variations in their incidence[59,60] and community variability in the recognition of general non-inflammatory bowel disease-related aphthous stomatitis, which itself is affected by gender, age and smoking status.[61,62] Registration of a condition as an extraintestinal manifestation may not include disorders which are an accompaniment to inflammatory bowel disease and which run a course often independent of disease activity or progression or which display an inherent autoimmune element, such as thyroiditis, haemolytic anemia or vitiligo. Further, inclusion of metabolically-associated problems consequent upon enteric disease such as nephrolithiasis, cholelithiasis and amyloidosis, may also not be registered as extraintestinal manifestations in many cases resulting in variable incidence reporting in the literature.

By contrast, although OFG is defined as granulomatous oral ulceration in the absence of clinical intestinal disease, half the patients will have inflammatory changes on ileo-colonoscopy in the absence of specific gastrointestinal symptoms, with two-thirds of such cases showing granulomata on gut biopsy.[63–65] Subclinical intestinal histological abnormalities are more likely to be found (if investigated) where there is an early age of onset of what is labeled initially as OFG or if there is more severe oral inflammation detected either on clinical examination or noted on oral mucosal biopsy.[66]

1.4. Management principles of OCD and OFG

Oral lesions in Crohn's disease may be asymptomatic and some may spontaneously resolve over time. The range of therapeutic options used in clinical decision-making for both OCD and OFG patients is shown as a management algorithm in Fig. 1, where severe labial and facial pathology requires more aggressive systemic therapy. Pediatric patients with OFG who also have coincident atrophy may often respond to dietary restriction of potential triggering agents including cinnamaldehyde, benzoate additives, carnosine, monosodium glutamate, cocoa and sunset yellow, although there are no available trial data beyond case reports concerning their dietary exclusion.[44,67,68] In symptomatic cases, treatment can often be simple and non-specific with analgesia and topical therapies, Beclomethasone mouth washes and 5-ASA ointments or sprays.[69] The range of treatments normally available for symptomatic Crohn's disease may also be used in those with very symptomatic OCD as well as part of a progressive treatment program in patients with OFG, particularly where there is oral disfigurement by fibrosing granulomatous disease or where painful recalcitrant ulceration is unresponsive to basic therapies.

Alternatives in the treatment of deep painful ulcers include the use of slow-release, highly concentrated intralesional steroid therapy with or without mandibular nerve blockade.[70] In unresponsive cases, topical tacrolimus at low concentration (0.5 mg/kg) is recommended where it has also been reported to be successful in severe lip swelling, resulting in minimal tachyphylaxis and systemic absorption, although there is reported rebound symptomatology after its cessation.[71,72] Systemic steroids are of value in resistant cases although when used alone they have been reported as providing remission in only half the patients with only a limited effect on lip swelling.[73] Their long-term use is contraindicated in children because of the risk of growth retardation and in unresponsive patients where steroid sparing is required, biologic therapies have been used with success, including Infliximab,[74,75] and Thalidomide[76] with or without the addition of methotrexate[77] and other steroid-sparing agents with anti-granulomatous properties including the anti-leprosy drug clofazimine.[78]

1.5. Summary

The definition of OFG is conventionally used to describe patients who present with granulomatous inflammation of the oral cavity without overt clinical evidence of intestinal inflammation. Its global incidence is rising partly because of an increased awareness of the diagnosis particularly in the pediatric population. At the same time, the incidence of Crohn's disease in high prevalence areas such as Northern Europe and the United states is falling explaining the paradoxical increase in OFG diagnosis.[27,79] Granulomatous oral ulceration is a specific biopsy finding with defined differential diagnoses where the clinical separation of OFG and OCD is important since the natural history of these conditions varies along with their presumed aetiopathogenesis.

Although many patients presenting with oral lesions in such circumstances are managed by dermatological and dental experts, both gastroenterologists and coloproctologists working

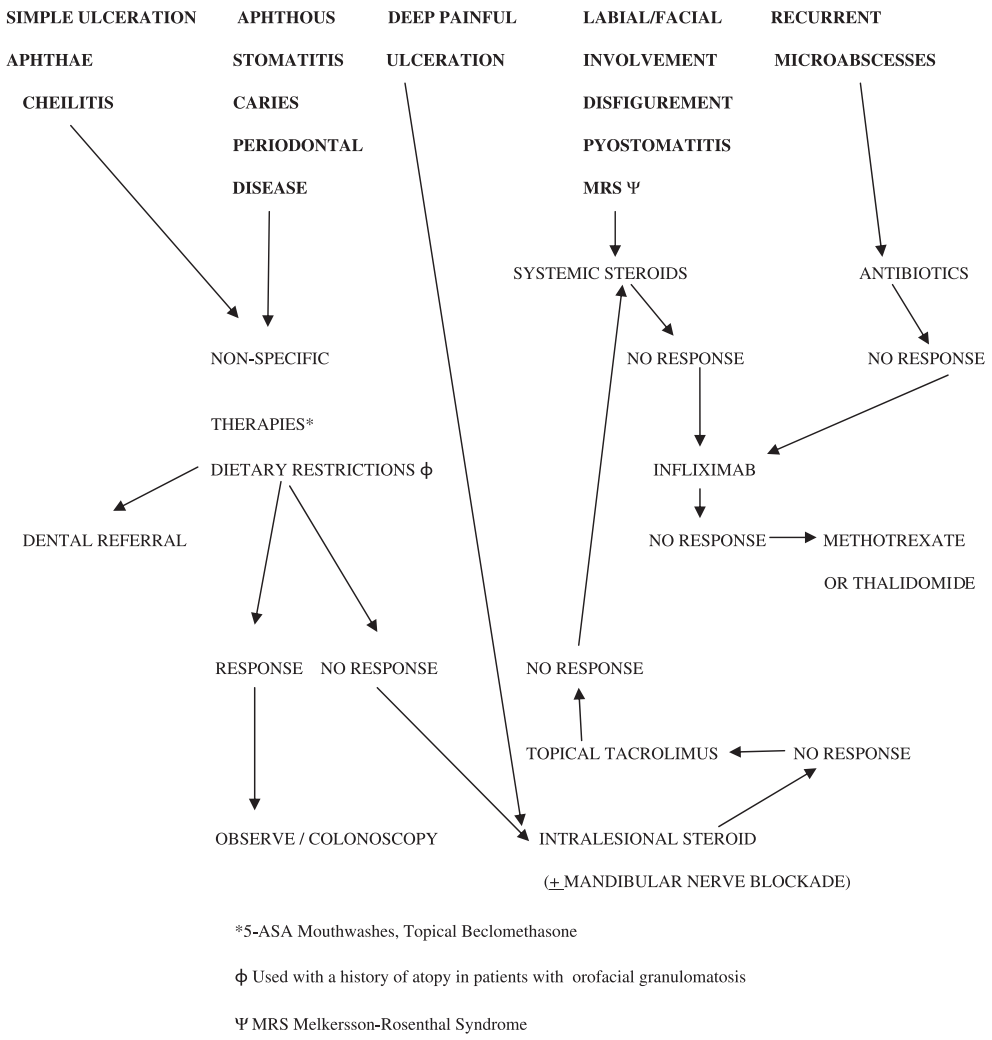

Figure 1 Management algorithm for patients with both OFG and OCD presenting with granulomatous oral ulceration.

in multidisciplinary inflammatory bowel disease clinics must be clinically familiar with the range of disorders which constitute the differential diagnosis once granulomatous oral disease has been confirmed.[3,80] Frequently oral disease is subclinical and self-resolving, where specific disease patterns appear to distinguish OFG from true OCD and where biopsy is only diagnostic if taken into consideration with the overall clinical picture. Oral disease in Crohn's is frequently not considered specifically as an extraintestinal maninfestation and is often inadequately documented so that its association with the prospective development of intestinal disease is relatively poorly understood. Depending on the dedication towards diagnosis and oral examination, the incidence of demonstrable oral pathology in patients with Crohn's disease can be relatively high with the clinical pattern currently providing a relatively clear separation from patients presenting with OFG.[8,64,81,82] It is recommended that there should be expert evaluation of the oral cavity both in patients with established Crohn's disease and those where Crohn's disease is suspected by virtue of its oral presentation or where OFG is diagnosed by exclusion. A greater liaison is required between medical and dental clinicians in order to better define the diagnostic separation and multi-disciplinary management of these patients.

Statement of authorship

AZ conceived the manuscript, structured the design of the review and helped draft the manuscript.

S B-H helped to draft the manuscript and provided advice.

M B-G helped to draft the manuscript and assisted in table construction.

RE helped to draft the manuscript and assisted in table construction.

Conflict of interest

No author has any declared conflict of interest in this publication.

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