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TRIAD OF PEDIATRIC OROFACIAL GRANULOMATOSIS, CROHN'S DISEASE AND INFLIXIMAB – A SYSTEMATIC REVIEW

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ABSTRACT

Background: Crohn's disease (CD), a kind of inflammatory bowel disease (IBD), is a systemic illness that often affects extraintestinal organs in addition to the gastrointestinal (GI) tract. Up to 24% of IBD patients experience extraintestinal manifestations (EIMs) prior to the development of intestinal symptoms, which can have a significant impact on their quality of life. The rare disorder known as orofacial granulomatosis (OFG) is characterized by the histologic finding of noncaseating granulomas in the oral mucosa and face on tissue biopsy, leading to chronic swelling. Less than 1% of CD patients have OFG, and biopsy is the most reliable way to make the diagnosis. While some view OFG as a separate condition without a systemic granulomatous disorder, others see it as a more comprehensive diagnosis that includes isolated OFG as well as a potential sign of sarcoidosis or CD. OFG frequently has a chronic and deforming course, which makes it very challenging to treat and eventually lowers the quality of life for those who are afflicted. In oral medicine, they are used to treat a number of ailments. For the treatment of complicated oral disorders such as Sjogren's disease, pemphigus vulgaris, and mucous membrane pemphigoid, biologics are increasingly advised. TNF-α inhibitors, such as adalimumab and infliximab, have also been shown to be effective in treating orofacial granulomatosis (OFG) and oral Crohn's disease. Six Nevertheless, little is known about how these substances affect the oral cavity and dental care.

Material and Methods: Major databases such as Medline were explored detailed literature search in resulting in a systematic review pertaining to Effective treatment of pediatric orofacial granulomatosis secondary to Crohn's disease with infliximab.

Results: Five original research scientific articles dated between 2020 – 2024 pertaining to mentioned topic were highlighted.

Conclusions: As a crucial early marker of underlying Crohn's disease, pediatric orofacial granulomatosis (OFG) requires extensive biopsies, ongoing surveillance, and interdisciplinary cooperation. Biologic therapy using infliximab provides a very effective way to alleviate symptoms and stop long-term structural orofacial damage in extreme situations. By identifying oral symptoms, keeping an eye on patients taking biologics, and working closely with medical specialists to guarantee thorough patient management, dental professionals play a critical role in this care network. Detailed information regarding the Effective treatment of pediatric orofacial granulomatosis secondary to Crohn's disease with infliximab is discussed in this systematic review.

Key word: Orofacial granulomatosis, Inflammatory bowel disease, Crohn's disease; infliximab; hypersensitivity; inflammatory disorders

Introduction

Orofacial granulomatosis is a chronic inflammatory disease that relapses and remits. Its phenotypic appearance is comparable to that of various other granulomatous disorders, including Crohn's disease. Subtle pathological and clinical variations, however, support its classification as a distinct disease entity. The efficacy of treatments for orofacial granulomatosis has been evaluated in earlier research. The interventions were divided into four categories: pharmaceutical, surgical, psychological, and dietary. To effectively manage each patient, a variety of therapies are frequently needed. There is strong evidence that the severity of an illness is influenced by nutrition. Topical, intralesional, and/or systemic treatment may be considered for patients whose disease cannot be managed by dietary modification alone.

IBD includes two immunologically based chronic clinical entities: ulcerative colitis (UC) and Crohn's disease (CD). Any section of the gastrointestinal system, most frequently the terminal ileum or the perianal area, might be affected by CD in a discontinuous manner, which can result in transmural inflammation. While UC is defined by mucosal inflammation and is restricted to the colon, CD is frequently linked to comorbidities such as abscesses, fistulas, and strictures. Immune responses, microbial flora, environmental variables, and genetic components are the main causes of IBD. Dysregulated immune responses, changes in the microbiota, and genetic and environmental variables combine in a very complicated way to develop IBD, but none of these factors alone is likely to be the cause of the illness. Although bowel symptoms are the most common, these illnesses can also cause extraintestinal problems, such as oral cavity involvement. Abdominal pain, diarrhea, rectal bleeding, weight loss, and indications of malnutrition are frequently linked to CD and UC.

During the course of their illness, about one-third of IBD patients experience extraintestinal symptoms. The biliary tract, joints, skin, and eyes are the most frequent extraintestinal symptoms. Although a number of explanations, including infection, genetics, and allergies, have been proposed, the exact origin of OFG is still unknown. A genetic predisposition has been assessed; some have indicated that the disease may run in families and that patients frequently express certain HLA antigens in comparison to the general population, which may indicate autosomal dominant transmission with incomplete penetration and translocation at chromosome 9p11. Resolving symptoms and improving clinical appearance are common goals of treatment for OFG. Treatment varies, and there are no national guidelines. A diet devoid of cinnamon and benzoate, topical or intralesional corticosteroids, hydroxychloroquine, dapsone, danazol, thalidomide, and antibiotics are among the treatment possibilities.

Due to the disease's chronic relapsing nature and the serious side effects of long-term steroid use, the use of systemic corticosteroid treatment is restricted. There is worry that the radiation used to diagnose and track inflammatory bowel disease increases the risk of lymphoma, which is already elevated. This is especially important for young children who will be monitored for the rest of their lives. The use of MRI as an imaging technique for inflammatory bowel disease is probably going to increase. TNF-α plays a role in the pathophysiology of numerous inflammatory and autoimmune diseases and is arguably the most important regulator of inflammation. Among the first biologics to be created were anti-TNF treatments, such as etanercept, certolizumab pegol, golimumab, adalimumab, and infliximab.1 Etanercept is a TNF-α receptor fusion protein, certolizumab pegol is a monoclonal antibody fragment specific to TNF-α, and infliximab, adalimumab, and golimumab are anti-TNF-α monoclonal antibodies. These medications are frequently used to treat Crohn's disease, ankylosing spondylitis, and rheumatoid and psoriatic arthritis (RA/PA).

Material And Methods:

"Orofacial granulomatosis" AND "Crohn's disease" AND "infliximab'' were the words used in MEDLINE database using advance search strategy targeting different article categories between 2020 to 2024. The result was 58 articles, out of which we selected 5 articles based in the inclusion criteria. Inclusion criteria was of case studies and scientific literature between 2020-2024. Exclusion

criteria was of scientific literature irrelevant to the specific search. This systematic review was conducted to determine importance of Effective treatment of pediatric orofacial granulomatosis secondary to Crohn's disease with infliximab following the guidelines of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). PubMed, Lilacs, Embase, Scopus, and Web of Science were the source of electronic databases. The search strategy used Boolean operators (AND and OR): [ALL ("Orofacial granulomatosis") AND (inflammation OR crohns OR pathology OR pediatric OR hypersensitivity) AND (infliximab)]. The following data were collected: first author, year, country of study, type of study and outcome. The quality of studies was assessed using the STROBE (Strengthening the Reporting of Observational Studies) checklist.

RESULTS: Five articles were included in this systematic review based on the selection criteria. We analyzed and mentioned in the five articles reviewed. This included only relevant research articles and excluded articles pertaining to nonspecific search terms.

Table 1 – An overview

Author	Title	Journal	Outcome
Maria R Galdiero, Filomena Maio, Francesco Arcoleo, Elisa Boni, Laura Bonzano, Luisa Brussino, Mauro Cancian, Luigi Cremonte, Stefano R Del Giacco, Amato De Paulis, Aikaterini Detoraki, Davide Firinu, Donatella Lamacchia, Stefania Loffredo, Eustachio Nettis, Roberta Parente, Paola Parronchi, Giovanni Pellacani, Angelica Petraroli, Giovanni Rolla, Riccardo Senter, Massimo Triggiani, Gianfranco Vitiello, Giuseppe Spadaro, Maria Bova	Orofacial granulomatosis: Clinical and therapeutic features in an Italian cohort and review of the literature	Galdiero MR, Maio F, Arcoleo F, Boni E, Bonzano L, Brussino L, Cancian M, Cremonte L, Del Giacco SR, De Paulis A, Detoraki A. Orofacial granulomatosis: Clinical and therapeutic features in an Italian cohort and review of the literature. Allergy. 2021 Jul;76(7):2189-200. doi: 10.1111/all.14799.	OFG is a rare and neglected disease showing multiple clinical phenotypes. There is a need to establish registry databases and address challenges of long-term management.
Kristen L. Chen MD, Daren A. Diiorio MD, Yvonne E. Chiu MD, Olayemi Sokumbi MD	Pediatric patients with orofacial granulomatosis likely to subsequently develop intestinal Crohn's disease: Brief Report	Chen KL, Diiorio DA, Chiu YE, Sokumbi O. Pediatric patients with orofacial granulomatosis likely to subsequently develop intestinal Crohn's disease: Brief Report. Pediatric Dermatology. 2020 Nov;37(6):1162-4. doi: 10.1111/pde.14390	The continues debate regarding whether OFG is a distinct clinical disorder or a manifestation of orofacial Crohn's disease. This indicates that gastroenterology evaluation with long-term monitoring for intestinal Crohn's disease is warranted.
Adnan Kurtovic, Julie A Bass, Kimberly A	Painless lip swelling in a child	Kurtovic A, Bass JA, Horii KA. Painless lip	This dermatological

Horii		swelling in a child. Pediatric dermatology. 2020 Sep;37(5):e69-70. doi.org/10.1111/pde.14247	presentation serves as a critical diagnostic clue that strongly correlates with underlying gastrointestinal conditions, specifically pediatric Crohn's disease
Michele Campigotto, Francesca Priotto, Cinzia Francesca Tonello, Fabio Monica, Saveria Lory Crocè	Efficacy and Safety of Upadacitinib and Vedolizumab Combination for Refractory Orofacial Granulomatosis Associated with Panenteric Crohn's Disease: A Case Report	Campigotto M, Priotto F, Tonello CF, Monica F, Crocè SL. Efficacy and Safety of Upadacitinib and Vedolizumab Combination for Refractory Orofacial Granulomatosis Associated with Panenteric Crohn's Disease: A Case Report. Reports. 2025 Mar 23;8(2):37. doi: 10.3390/reports8020037.	This is a unique case of orofacial granulomatosis associated with pan-enteric Crohn's disease successfully treated with Upadacitinib.
Siri A Urquhart, Grace Y Kim, Katelyn R Anderson 2, Victor G Chedid 1	Orofacial Granulomatosis and Crohn's Disease: A Case Series	Urquhart SA, Kim GY, Anderson KR, Chedid VG. Orofacial Granulomatosis and Crohn's Disease: A Case Series. ACG case reports journal. 2024 Nov 16;11(11):e01559. doi: 10.14309/crj.0000000000001559.	OFG may be characterized by partial response, often requiring long-term therapy. Additional investigations into novel treatments may improve future clinical outcomes.

Discussion

Orofacial granulomatosis (OFG) is a rare group of chronic immune-mediated diseases characterized by granulomatous inflammation of the oral or perioral tissues.1

It can be idiopathic or associated with other immune mediated diseases, A delayed hypersensitivity reaction with a predominant Th1-mediated immune response seems to be the etiopathogenic mechanism.2

The relationship between OFG and Crohn's disease (CD) is unclear: the oral cavity is a potential site involved, and it is usually more severely affected during active disease. However, up to 30% of patients may present oral lesions despite disease control.3

bOrofacial granulomatosis (OFG) is a term devised to cover a variety of granulomatous, oedematous conditions of the lips and face. It was described as granulomatous cheilitis as part of the Melkersson–Rosenthal syndrome.4

Current research indicates that not all orofacial granulomatosis (OFG) cases progress to Crohn's disease, challenging earlier consensus.5

Recent findings suggest OFG may constitute a distinct inflammatory bowel condition, potentially classifying cases into three groups: classical oral Crohn's, bowel-associated OFG, and OFG without bowel involvement.6

Other granulomatous diseases suggested as causative include mycobacterial infection, sarcoidosis, although in idiopathic OFG is allergy and dental hygiene products and food-associated allergens.7

The prevalence of OFG is unknown, but a figure of 0.8% has been suggested.8

The characteristic oral and facial features are lip swelling, angular cheilitis, swelling of the cheek, full thickness gingivitis, fissured tongue, mucosal tags, linear oral ulceration and a cobblestone or basket of eggs appearance of the buccal mucous membrane.9

Studies suggest the occurrence of the disease in families and frequent expression of some HLA antigen possibility of autosomal dominant transmission with incomplete penetrance and translocation at chromosome 9p11.10

The association between OFG and HLA has been investigated and three available studies do not show a strong link between HLA and pathogenesis of OFG.11

Interestingly, a meta-analysis of published results of the pooled sera of 730 patients with CD shows that patients with HLA-A2 carry a comparatively higher risk.12

Hypersensitivity to food, known to evoke a delayed type hypersensitivity reaction, especially contact hypersensitivity. This further supported by the fact that approximately 12–60% of the patients with OFG are atopic.13

Crohn's disease is a disorder affecting 'the mouth to the anus, isolated from of the upper gastrointestinal tract and oral Crohn's disease (OCD) is a relatively uncommon finding where understanding of its pathogenesis is evolving.14

The term orofacial granulomatosis (OFG) is to define the presence of granulomatous oral ulceration without intestinal involvement, although it is recognized that granulomatous mouth ulcers may predate intestinal involvement in Crohn's disease.15

Crohn's disease presents with a range of oral lesions, which includes diffuse lip and buccal mucosal swelling, oral cobble stoning, buccal sulcus ulceration, and mucosal tags.16

Cobble stoning is typically located on the posterior buccal mucosa and can 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.17

Many of these lesions may be preceded by painless gingival enlargement and this finding in its earliest stages should be distinguished from other known drug related, systemic and idiopathic causes of gingival hypertrophy.18

Non-specific lesions are distinguished from OCD and OFG by collagen deposition and MMP-3/TIMP-2 over-expression, as these markers are absent in true oral Crohn's or orofacial granulomatosis.19

Oral Crohn's disease presents with angular cheilitis, perioral rashes, and aphthous stomatitis, affecting up to 60% of patients and acting as the first sign in 5–10% of cases.20

OFG differs from OCD by causing persistent labial and facial swelling, presenting with granular, erythematous lips and distinct aphthous or deep buccal ulceration types.21

Pyostomatitis vegetans is characterized by soft pustular mucosal folds and eosinophilic microabscesses, lacking immunoglobulin deposition, which separates it from pemphigus vulgaris.22

Melkersson–Rosenthal syndrome, a rare OFG variant, features orofacial swelling, fissured tongue, and delayed facial paralysis, with its incomplete form responding to Infliximab.23

The range of therapeutic options used in clinical decision-making for both OCD and OFG patients, where severe labial and facial pathology require more aggressive systemic therapy.24

Pediatric patients with OFG who also have coincident atrophy may often respond to dietary restriction of potential triggering agents.25

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.26

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.27

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.28

For steroid-unresponsive cases, topical tacrolimus (0.5 mg/kg) successfully reduces severe lip swelling with minimal systemic absorption and tachyphylaxis, though symptoms may rebound after cessation.29

Long-term steroid use is contraindicated in children due to growth retardation risks; therefore, unresponsive patients requiring steroid-sparing alternatives are successfully treated with biologics like Infliximab, Thalidomide, or clofazimine.30

Orofacial granulomatosis (OFG) is significantly more often diagnosed by a multidisciplinary team, with stomatologists and dentists being the most frequently involved specialists, followed by another speciality.31

Patients frequently experience a consistent diagnostic delay ranging from months to years, with some individuals waiting up to 5 years to receive a final diagnosis of OFG.32

A differential diagnosis of Crohn's disease was considered in children with OFG, with 40.4% ultimately being diagnosed either at presentation or within 3 to 36 months later, while sarcoidosis, tuberculosis, and allergy/atopy were far less common.33

Among children presenting with OFG, 12.1% exhibited perianal disease and 6.4% had a known family history of Crohn's disease.34

Both the presence of perianal disease and a positive family history of inflammatory bowel disease were significantly associated with an increased risk of developing Crohn's disease in pediatric OFG patients.35

The main classes of biological therapies in widespread use include: i) anti-tumour necrosis factor-alpha (TNF-α) inhibitors; ii) anti-interleukin (IL) therapies; iii) anti-integrin inhibitors; iv) anti-B cell inhibitors; and v) anti-T cell inhibitors.36

Many of these agents are monoclonal antibodies, denoted by the suffix -mab, that target a specific cytokine, infliximab which targets TNF- α, or a cell marker, for example, rituximab which targets CD20 which is expressed solely on B cells.37

TNF-α is perhaps the most significant regulator of inflammation and is involved in the pathogenesis of many inflammatory and autoimmune conditions.38

Infliximab, adalimumab and golimumab are anti-TNF-α monoclonal antibodies, certolizumab pegol is a monoclonal antibody fragment specific to TNF-α, while etanercept is a TNF-α receptor fusion protein.39

These drugs are widely used in the management of rheumatoid and psoriatic arthritis, ankylosing spondylitis and Crohn's disease. Ustekinumab is used in the management of psoriasis, PA, ulcerative colitis and Crohn's disease.40

Treatment often aimed at symptom resolution and clinical appearance. National guidelines are absent and treatment is varied. It includes, intralesional or topical corticosteroids, hydroxychloroquinine, dapsone, danazol, thalidomide.41

The use of long-term systemic corticosteroid treatment is limited due to the relapsing chronic nature of the disease and the significant side effects associated with long-term steroid use.42

New guidelines from the ECCO-ESGAR suggest that MR enterography/enteroclysis has a similar diagnostic accuracy to CT, with the enormous advantage of not imparting ionising radiation.43

However, modalities using ionising radiation such as barium follow through and CT are still used frequently, probably as a consequence of the limited availability of MRI in some hospitals.44

It requires a re-evaluation with a gastroenterologist as soon as the lesions appear. In the case of nonresponse, intralesional injection of corticosteroids is prescribed.45

If the patient's symptoms do not improve, a systemic approach with corticosteroids is required. In severe cases, for example of visualizing oral CD or diluting it to treat aphthous stomatitis, treatment with biologic drugs has obtained satisfactory results.46

However, in the case of our patient, first-line treatment was based on the use of systemic steroids and maintenance therapy with thiopurine, which was complicated and formed development of steroid dependence and complications in the form of osteoporosis.47

The step up approach was adopted, taking into account the history of suspected pulmonary tuberculosis in 2015, therapy with vedolizumab was started, which was not effective enough, and the next step was to start therapy with infliximab.48

Infliximab is a chimeric monoclonal IgG1 antibody that binds to both soluble and membrane TNFa and inhibits the binding of TNFa to its receptors.49

The effectiveness of infliximab in extraintestinal manifestations of IBD, in particular in oral CD, has been shown more than once in other works.50

Conclusion

Orofacial granulomatosis (OFG) is a long-term inflammatory condition that primarily affects the lips, although it can also affect the gingivae, buccal mucosa, floor of the mouth, and several other areas of the oral cavity. The term OFG was first used to characterize patients with oral lesions similar to those of Crohn's disease (CD) but no obvious intestinal involvement. The evidence indicates treatment with an anti-TNF agent (mainly infliximab) is the most recommended therapeutic option for granulomatous cheilitis (with or without CD) after failure of conventional treatments. Nevertheless, despite extremely high dosages and supra-therapeutic drug levels, the effectiveness of TNF blocking with infliximab was totally lost in our patient. In these situations, it might be presumed that cytokines other than TNF are responsible for the damage. By stimulating several proinflammatory cytokines, IL-12 and IL-23 are associated with the synthesis of IFN-γ, a crucial mediator of inflammation in peripheral tissues, including orofacial mucosa. Therefore, the alternative use of other biological agents, such as ustekinumab, a monoclonal antibody against interleukins 12/23 with demonstrated efficacy in CD and psoriasis, is appealing for treating granulomatous cheilitis. The efficacy of ustekinumab in inducing remission of severe and recurrent granulomatous cheilitis in CD patients is being reported for the second time. Furthermore, it should be mentioned that infliximab should never be utilized in OFG cases where myeobacteria are the causative agent. TNF-a is required for granuloma formation, which in, for example, tuberculosis or leprosy, represents the effort of the host to eontrol myeobacterial infection effieientiy. Therefore, it is necessary to screen for mycobacterial infections before using TNF-α-blocking medications. When other therapeutic techniques have failed, infliximab may be a useful treatment choice for persistent OFG when such conditions have been ruled out.

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