

Orofacial Granulomatosis: A Review

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Abstract

Orofacial Granulomatosis (OFG) is an uncommon clinicopathological entity characterized clinically by the presence of persistent enlargement of the soft tissues of the oral and maxillofacial region and histologically by non-caseating and non-necrotizing granulomatous inflammation. The term 'orofacial granulomatosis' has been introduced to denote the group of various disorders, including Melkersson-Rosenthal syndrome and granulomatous cheilitis and has been noted to be associated with Crohn's disease, Sarcoidosis and infectious diseases such as Tuberculosis. Although, various etiological agents such as dental materials, food additives and microbial agents have been recommended in the disease process. Treatment of orofacial granulomatosis is by corticosteroids but it's not so efficient. It is more important to identify the pathogen first to specify the appropriate treatment line.

Keywords— *orofacial granulomatosis, Melkersson Rosenthal syndrome, crohn,s disease.*

Introduction

Orofacial granulomatosis term was introduced by Wiesenfeld in 1985¹. Granulomatosis is any condition characterized by the formation of multiple nodules or granulomas in soft tissues. It encompasses Melkersson Rosenthal syndrome and Cheilitis granulomatosa¹. The true prevalence of this disease is unknown but is suggested to be 0.8% (Mahler and Kiesewetter, 1996)³. It is principally a condition of children and young adults, common in both genders² with slight female predilection. It is also associated with oral ulceration, gingival overgrowth and a cobblestone appearance of the buccal mucosa⁴. The diagnosis can be confirmed by histopathological identification of non-caseating granulomas⁵. The precise etiology of Orofacial granulomatosis is unknown. Genetics, allergies (food, dental materials), microbial agents or immunology were suggested as potential causative agents^{6,7}.

Definition and its associated to other granulomatous disorders

Orofacial granulomatosis is an uncommon disorder¹ but is increasingly recognized. Orofacial granulomatosis (as defined by Wiesenfeld in 1985) is the specific histological finding of granulomas in mucosal or skin biopsies taken from the mouth or face in the absence of a recognised systemic condition known to cause granulomas.

Orofacial granulomatosis includes a group of disorders showing chronic, non-caseating granulomatous lesions involving the perioral tissue of face and oral mucosa and whose diagnosis is based on exclusion of possible systemic diseases such as Tuberculosis, Sarcoidosis^{4,8,9}. It can cause significant cosmetic and functional problems but can be prevented if diagnosed early and treated promptly.¹⁰ Most common diseases of orofacial granulomatosis involving head and neck region⁸ are

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1. Melkersson Rosenthal syndrome
2. Sarcoidosis
3. Crohn's disease
4. Midline lethal granuloma

5. Wegener's granulomatosis

MELKERSSON ROSENTHAL SYNDROME (MRS)

It is a neuro-muco-cutaneous disorder involving both the intermittent orofacial innervations and mucocutaneous tissues in a pathosis of complex origin characterized by recurrent oedema, facial palsies and nerve dysfunctions frequently associated with plicated tongue^{11,12}. However, many patients did not manifest all signs of this triad. Monosymptomatic or oligosymptomatic are two forms in which only one or two features of the triad are present commonly.^{13,14}

Melkersson reported a case describing facial palsy and orofacial oedema in 1928 with symptoms of facial palsy and orofacial swelling. Subsequently, Rosenthal in 1932 described the triad of persistent lip or facial swelling, recurrent facial oedema, swelling and fissured tongue.¹⁵ Thus, the term Melkersson Rosenthal syndrome was derived by Hornstein et al and Worsae et al and reported forms of Melkersson Rosenthal syndrome as monosymptomatic/ oligosymptomatic which was described by Miescher in 1945 as Cheilitis granulomatosis.¹⁶

It is manifested as orofacial oedema which affects the face, lips, gingiva, buccal mucosa or tongue.¹⁴ Upper lip swelling begins as the first symptom and follows lower lip swelling involving one or both cheeks.¹⁷ The enlarged lip appears cracked and fissured with reddish brown discoloration and scaling.¹⁸

SARCOIDOSIS

Sarcoidosis is described as a multisystem granulomatous disease of unknown origin characterized by the formation of uniform, discrete, compact, non-caseating epithelioid granulomas¹⁹. It is also known as Boeck sarcoid and Besnier-Boeck-Schaumann disease²⁰. Jonathan Hutchinson, an English surgeon- dermatologist, reported the first case of sarcoidosis in 1875, but this term sarcoidosis was introduced later by Boeck in 1899, which in Greek means, "flesh-like" condition. The etiology is unknown. Most common feature is pulmonary infiltration like dry cough, dyspnoea and Lofgren syndrome.²⁵ On the palate and buccal mucosa, the lesions are bleb like, containing a clear yellowish fluid or as solid nodules²¹. It also appears that Sarcoidosis may produce diffuse destruction of bone.

CROHN'S DISEASE (CD)

It encompasses a group of disorder with specific clinical and pathological features, characterized by focal asymmetric, transmural and occasionally granulomatous inflammation primarily affecting the gastrointestinal tract.³⁶ It has now been described as a pan-electric disease that can affect any part of the gastrointestinal tract, from mouth to anus²². Idiopathic inflammatory bowel disease affecting the small intestine was first reported in 1932 by Crohn and his workers. The first report of Crohn's disease affecting mouth was made by Dudeney in 1969, describing a tag on the buccal mucosa of a 36 year old patient.

Young patients with recurrent painful intraoral ulcerative lesions with no signs of systemic disease, apart from weight loss are affected. Clinical manifestations of non-specific and specific lesions include²³

- Cobblestone appearance of buccal mucosa.
- Epithelial tags and folds.
- Full thickening and swelling of the gingiva.
- Linear aphthous ulceration.
- Redness of attached gingiva extending to mucosal margins.
- Persistent enlarged rubbery lip swelling.²³

MIDLINE LETHAL GRANULOMA

It is the ulcerative process that occurs in the nose characterized by epithelium and cartilage loss with crusting resulting in loss of nasal structure, support and ultimately causing cosmetic and functional deformity.¹¹ Midline destructive lesions of the face were first reported in 1897. Stewart et al reported 10 cases of a chronic destructive midfacial process in 1922 and named as Midline lethal granuloma.²⁴ The common presenting symptoms include chronic rhinosinusitis refractory to treatment and midline lesion destroy normal sinonasal anatomy.²⁴

WEGENER GRANULOMATOSIS

It is a condition associated with generalised vasculitis and was reported by Heinz Klinger and Frederick Wegener in 1936²⁵. The classical tissue abnormality in all organs affected by Wegener granulomatosis is

inflammation with granuloma formation against a non-specific inflammatory background.²⁶ Hyperplastic granular gingivitis or “strawberry gingivitis” is a rare manifestation of Wegener’s granulomatosis, but it is nearly pathognomic for this multisystem autoimmune vasculitis²⁶.

AETIOPATHOGENESIS

Although a number of possible causative agents have been associated to orofacial granulomatosis²¹, the actual etiopathogenesis remains unknown.

HEREDITARY AND GENETIC PREDISPOSITION

According to the available literature, there is no adequate data that shows that orofacial granulomatosis has a definite genetic background.^{4,27} An association between orofacial granulomatosis and human leukocyte antigen (HLA) has been seen and the two studies present do not depict a strong link between HLA and pathogenesis of orofacial granulomatosis.²⁷

FOOD ALLERGY AND ALLERGY TO DENTAL MATERIALS

Various food substances and food additives²⁴ have been suggested to be either the cause or the predisposing even in orofacial granulomatosis. A wide range of hyper sensitivities have been recorded in orofacial granulomatosis patients including dental restorative materials²⁸, toothpastes and other dental hygiene products²⁹, cocoa and chocolate²⁹, cinnamon compounds, carvone, carbone piperitone, aspartate^{29,30,31}, carmosine and sun yellow dye³⁰, monosodium glutamate³⁰, benzonates^{30,31} and tartrazine. Cinnamon and benzonate compounds have been suggested to be most common triggers^{29,30,31}

INFLAMMATORY/IMMUNOLOGICAL FACTORS

Description of granulomatous inflammation of orofacial granulomatosis has lead to contrary and incongruous results. Its uncertain whether lesional T cells of orofacial granulomatosis depict clonal expansion as a outcome of chronic antigen stimulation²⁷. Studies on the expression of cytokines and chemokines in orofacial granulomatosis lesions have found a predominant Th1-mediated immune response²⁷.

INFECTIONS AND MICROBIAL FACTORS

The significance of microbiological factors in the

causation of orofacial granulomatosis follows notation of infective agents associated with chronic granulomatous conditions such as Crohn’s disease, sarcoidosis and tuberculosis. Several authors have inspected the probable role of microbial factors in initiating the immune response of orofacial granulomatosis, involving M.Tuberculosis, Saccharomyces cerevisiae, M.Paratuberculosis, Candida albicans and Streptococcus Mutans.

CLINICAL FEATURES

Labial enlargement and sometimes oral ulcers are primarily the clinical manifestations of orofacial granulomatosis, but numerous other features can also be seen.

LABIAL ENLARGEMENT

It involves upper or lower lip or both^{10,32}. The swelling is often persistent but can be recurrent also each episode taking weeks to months³³. Non-tender in palpation, non-pitting at pressure and in consistency it may vary from soft to rubbery, labial mucosa can be erythematous and have granular appearance^{10,32,33}. Affected individuals may develop a lip licking habit that gives rise to consequential cheilitis with swelling, redness and drying of perioral skin³⁴.

ORAL ULCERS

The three preeminent forms of ulcer can be encountered in orofacial granulomatosis.³⁵ The major ulcers are linear and longitudinal at the depth of buccal or labial vestibule with raised borders. The less common second type of ulcer are superficial aphthous like ulcers with well circumscribed borders. These can appear on any oral mucosal surface. Lastly, the unusual type of ulcer associated with orofacial granulomatosis are described as pustules on the labial vestibule, anterior gingiva or at soft palate. They have similar appearance as pyostomatitis vegetans and are not clinically purulent.

MUCOSAL TAGS

In labial or buccal vestibule or in the retromolar region, pink or red painless tags of mucosa, akin to the raised borders of the chronic ulcers have been seen.

MUCOSAL SWELLING

The swollen and folded buccal and labial mucosa gives rise to cobblestoned appearance. It sometimes give rise to highly noticeable folds with an overlying normal

mucosa in the posterior area of buccal mucosa.

CERVICAL LYMPHADENOPATHY

In patient with severe orofacial granulomatosis tender or non-tender lymphadenopathy of variable size and rubbery consistency at later stages is seen. It can be localized or generalized.

GINGIVAL ENLARGEMENT

Diffuse or local painless enlargement of attached and or free gingiva can arise, sometimes preceding other facial and/or mucosal features by several weeks⁸. The gingiva appears granular with normal salmon pink to red in colour.

FISSURING OF TONGUE

Fissured tongue at dorsal surface can be seen. The fissures commonly are more pronounced on lateral aspect of dorsum.

FACIAL ERYTHEMA AND SWELLING

There can be persistent and/or recurrent swellings mainly in genial, zygomatic, perioral, periorbital and palpebral areas of face. These swellings are often soft in consistency and non-pitting at pressure.

FACIAL NERVE PALSY

Rarely paralysis of lower motor neuron of facial nerve may arise in orofacial granulomatosis. This apparently shows the formation of granuloma within the course of main stem of nerve. It is accompanied with fissured tongue and labial swelling indicative of Melkersson-Rosenthal syndrome.

DIAGNOSIS

The diagnosis of orofacial granulomatosis depends on the presence of relevant orofacial clinical findings, histopathologic evaluation of non-caseating granulomatous inflammation and the exclusion of systemic disorders causing similar manifestations. Endoscopy, blood chemistry and radiological evaluation are used to differentiate orofacial granulomatosis from crohn's disease, sarcoidosis, tuberculosis and foreign body reactions. Allergy testing in form of skin testing to various food stuffs and additives may also be carried out. There is no accord with respect the most appropriate measure or instrument to assess orofacial granulomatosis

disease severity/activity and monitor response to treatment.

TREATMENT

Spontaneous remission of orofacial granulomatosis is rare¹⁶. The main aim of orofacial granulomatosis treatment is to lessen cosmetically unwanted orofacial swelling and control painful mucosal ulceration, however treatment may not be always required if symptoms and/or signs are mild. The most reliable treatment of the disease remains to be explained cause of its unknown aetiology and the current approach is based upon symptomatic treatment.³³

Topical corticosteroids and immunosuppressant like tacrolimus applied directly onto the lips and oral mucosa have been reported to induce reduction of oral ulceration and labial swelling in small number of patients. Systemic corticosteroids and immunosuppressant, anti-tumour necrosis factor (TNF) agents like thalidomide, infliximab and adalimumab and other agents like anti leprotic agents, as well as surgical cheiloplasty and low-level laser therapy have been used as single or combined therapy with some positive, although overall inconsistent, results in a variety of cases. Intralesional injections of corticosteroid in the treatment of orofacial swelling were introduced in 1971. Initially low concentration triamcinolone acetonide (10mg/ml) was used, requiring multiple sessions (12 to20) of injections at approximately 2 week intervals in order to obtain a favourable clinical response. Similarly, the supporting results of diet modification like benzoate- and cinnamon- free diet reported by White et al. Miscellaneous drugs like methotrexate, minocycline, metronidazole, hydroxychloroquine and psychological support and counselling may be beneficial in developing coping mechanism and improving life quality.

Conclusion

Orofacial granulomatosis, being increasingly recognized nowadays, has become a topic of interest to all professionals and poses a great challenge to us at all levels starting from its diagnosis to the prognosis and treatment.

Regular clinical review is necessary to determine if there is any development of gastrointestinal involvement, and limited use of systemic steroids on long-term patient outcome are highlighted in literature. Current therapies available remain unsatisfactory. It seems that wide range

of patients on therapy would eventually experience a variable degree of reduction in orofacial swelling.

Etical Clearance: Taken By The Committee

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