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OROFACIAL GRANULOMATOSIS – A REVIEW

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ABSTRACT Orofacial Granulomatosis (OFG) is a rare clinicopathological entity characterized clinically by the presence of continuous 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 indicate the group of various disorders, involving Melkersson-Rosenthal syndrome and granulomatous cheilitis and has been noted to be associated with Sarcoidosis, Crohn's disease and infectious diseases such as Tuberculosis. But, various etiological agents such as food additives, dental materials 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 find the pathogen first to specify the appropriate treatment line.

KEYWORDS :

INTRODUCTION:

The recurrent chronic orofacial swelling can lead to significant cosmetic and functional problems and can be prevented if the disease is diagnosed initially and treated with no delay[1]. These recurrent orofacial swellings may be because of orofacial granulomatosis (OFG) such as Melkerson Rosenthal syndrome, Miescher"s Cheilitis, Sarcoidosis, Tuberculosis, Leprosy (Hansen disease, deep fungal infections, Crohn"s disease)[2-4]. The term orofacial facial granulomatosis is defined with insistent swelling of oral or facial tissues with histologic evidence[5] . It is a unique term showing the feasible of more than one underlying etiologies. The word „Orofacial granulomatosis" was alleged by Wiesenfeld et al in 1985 as a descriptive term for non-infectious granulomatous disorder of lips, face and oral cavity which are histologically associated with non caseating epitheloid granulomas and multinucleated Langhans type of giant cells within oral mucosa.[6] Presently, the term orofacial granulomatous includes a group of disorders showing chronic, non-caseating granulomatous lesions involves the perioral tissue of the face and oral mucosa and whose diagnosis is based on exclusion of possible systemic diseases such as Tuberculosis, Sarcoidosis.[7-9] Most regular diseases of Orofacial Granulomatosis which involves head and neck region[8]are

1. Melkerson Rosenthal syndrome
2. Crohn"s disease
3. Sarcoidosis
4. Wegener"s Granulomatosis
5. Midline Lethal Granuloma

Epidemiology:

The prevalence is unknown. OFG may occur at all age groups but appears to be most common in young adults. No racial or sex predilection has been demonstrated constantly. Recent literature from Sweden suggests geographic differences in epidemiology may exist[10]

Etiology:

The term 'etiology of orofacial granulomatosis' is used to elaborate diseases which have a different clinical manifestation but also have a relavant histopathological picture to nonspecific, noncaseating granulomatous inflammation. OFG is also considered a varied pathology or a manifestation of systemic disease[11,12]. The precise cause of OFG is still unaware, but several theories have been suggested including infection, hereditary factors and allergy. A genetic predisposition has been described in different studies; some of these recommended the circumstance of the complaint in the families and a constant expression of some HLA antigens among the cases compared with the normal population, conceivably of autosomal dominant transmission with deficient penetration and translocation at chromosome 9p11[13,14].

Etiopathogenesis:

Although a number of feasible causative agents have been associated to orofacial granulomatosis[15].

The etiopathogenesis of OFG remains elusive, although there are minor immunological changes detectable in a number of patients[16].

Hereditary And Genetic Predisposition:

According to the available literature, there is no acceptable data that shows that orofacial granulomatosis has a definite genetic background[7,17]. An association between orofacial granulomatosis and mortal leukocyte antigen (HLA) has been seen and the two studies present do not depict a strong link between HLA and pathogenesis of orofacial granulomatosis[17].

Inflammatory/immunological Factors:

Characterisation of granulomatous inflammation of OFG has route to inconsistent results. It remains unclear whether lesional T cells of OFG represent clonal expansion as a result of chronic antigen stimulation[17,18,19]. Studies on the expression of 4 cytokines and chemokines in OFG lesions have found a predominant Th1-mediated immune response[17,20].

Hypersensitivity reactions: Patients with OFG may have a

history of atopy, and there are occasional associations with food intolerance, e.g. monosodium glutamate and food preservatives[16] and chocolate[21.] Delayed hypersensitivity to dental materials has occasionally been implicated[22], and the removal of amalgam has caused reduction of swelling of buccal mucosa and lips of OFG in isolated cases[23].

Infections And Microbial Factors:
Infection by Mycobacterium paratuberculosis, once postulated in the etiopathogenesis of Crohn's disease and of OFG, appears not to be of significance[24].

Clinical Features:
Labial enlargement and sometimes oral ulcers are primarily the clinical manifestations of orofacial granulomatosis, but numerous other features can also be seen[25].

Labial Enlargement:
Labial enlargement involving upper or lower lip or both[1.]. The swelling is mostly persistent but can be recurrent also each episode taking weeks to months[26]. Non-tender in palpation, non-pitting at pressure and its consistency may vary from soft to rubbery, labial mucosa can be erythematous and have granular appearance[1,26,27]. Affected individuals may develop a lip licking habit that leads to consequential cheilitis with swelling, redness and drying of perioral skin[28].

Oral Ulcers:
The three preeminent forms of ulcer can be encountered in orofacial granulomatosis[29]. The significant ulcers are direct and longitudinal at the depth of buccal or labial vestibule along with raised borders. The less common alternate type of ulcer are superficial apthous like ulcers with well circumscribed borders. These can appear on any oral mucosal surface. Finaly, 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 same appearance as pyostomatitis vegetans and are not clinically purulent[25].

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[25].

Mucosal Tags:
The chronic ulcers have been seen on labial or buccal vestibule or in the retromolar region, pink or red painless tags of mucosa, akin to the raised borders[25].

Gingival Enlargement:
Diffuse or local painless enlargement of attached and/or free gingiva can happen, sometimes preceding other facial and/or mucosal features by several weeks[8]. The appearance of the gingiva is granular with normal salmon pink to red in colour[25].

Fissuring Of Tongue:
Fissured tongue can be seen on the dorsal surface. The fissures are more commonly present on lateral aspect of dorsum[25].

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[25].

Facial Erythema And Swelling:
The swellings can be persistent and/or recurrent mainly in genial, zygomatic, perioral, periorbital and palpebral areas of face. These swellings are mostly soft in consistency and non-pitting at pressure[25].

Cervical Lymphadenopathy:
Cases with severe orofacial granulomatosis have tender or non-tender lymphadenopathy of variable size and rubbery consistency at later stages is seen. It may be localized or generalized[25].

Histopathology:
Histopathology should always shows a chronic inflammatory infiltrate[30]. But it is considered a granulomatous entity, lower than half of patients have noncaseating granulomas, usually small and poorly defined, with lymphocytes surrounding epithelioid histiocytes[30,31]. Multinucleated giant cells can also be seen, with edema of the corium, lymphangiectasia and perivascular lymphocytic infiltration[32].

Diagnosis:
The diagnosis of OFG is based on histopathologic evaluation of non-caseating granulomatous inflammation and according to clinical manifestation of recurrent persistent orofacial swellings inappropriate to microorganisms or foreign objects. Endoscopy, blood chemistry, and radiological evaluations are denoted to differentiate OFG with non-caseating granulomatoses[33].

Differential Diagnosis:
The most frequent reason for labial swelling is trauma, infection, and angioedema which subside after removing the etiological factors and are transient in nature. A number of diseases can mimic characteristics of OFG especially persistent lip swelling such as Crohn's disease, sarcoidosis, cheilitis granulomatosa, Wegener's granulomatosis, granulomatous infections such as tuberculosis, leprosy and leishmaniasis deep fungal infections, amyloidosis, some soft tissue tumors, minor salivary gland tumors, Sjogren's syndrome, cysts, microcystic adnexal carcinoma and foreign body reactions[34,35-40].

Treatment:
Spontaneous remission of OFG is uncommon[3]. Treatment not indicated always if symptoms and/or signs are mild. Elimination diets to find and exclude dietary allergens have been advocated by some[41] and would seem justified if the patient has an identified food or food additive intolerance, for example, to monosodium glutamate, cocoa, carnosine, cinnamaldehyde, Carbone or sunset yellow.

Most cases, however, needs some medical intervention but the lip swelling can be difficult to resolve. Intralesional corticosteroids (e.g. triamcinolone acetonide 40 mg/mL) may cause some advancement in some but not all cases. Repeated injections may also have some success, however, as pain can limit the volume of triamcinalone injected, bilateral mental nerve blocks may be needed. The long-term result of intralesional corticosteroid therapy is not unknown. Clofazimine, an antileprosy agent with anti-inflammatory and especially antigranulomatous properties appears effective. In one study, treatment with clofazimine (100 mg four times weekly for 3–11 months) was related with complete remission in five of 10 patients and clinical improvement in further three patients with moderate constant swelling[42]. In addition, clofazimine is effective and also been recommended for cases with severe cheilitis granulomatosa[43].

In acute swelling, cold compresses, lip lubricants and emollients can be indicated[3]. Ulceration of the oral mucosa, mucosal tags, and cobblestoning are mostly managed with topical corticosteroids and are rarely severe enough to require systemic agents. Small orofacial swelling can be cured with topical corticosteroids, calcineurin inhibitors or both. Oral

candidiasis is the most repeated adverse event of topical therapy[31].

Systemic corticosteroids mostly have short-lived benefits, and chronic use is associated with undesirable adverse events. Other systemic immunosuppressants are probably a safer option in the long-term, mainly thalidomide, mofetil, mycophenolate, azathioprine, infliximab and adalimumab[44].

Surgery should only be indicated in severely disfiguring cases, after medical treatment has proven inadequate, preferably during a quiescent phase of the disease[7].

Follow-up is most important, since treatment is usually performed in a long-term basis. Prognosis is good, but patients must be informed that recurrence is more common and often unexplained[45]. Clinical outcome is unpredictable, however, persistent orofacial swelling can be excluded when OFG is diagnosed and treated early on[7,30].

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.

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