Orofacial Granulomatosis: A Clinicopathologic Correlation

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Abstract Orofacial granulomatosis is an uncommon disorder, but has been increasingly recognized in the past decade. It causes significant morbidity in the patient including oral ulcerations, enlargement of soft tissues which are often persistent and painful. This necessitates early medical intervention. We report one such case of a female patient who presented with a persistent upper lip enlargement. She had visited multiple general dental practitioners and general physicians but was undiagnosed. Ultrasonography proved an adjunctive tool in diagnosis. She was treated with a combination of topical and intra-lesional steroids. A 1 year follow-up did not show any evidence of recurrence.

Keywords Lip swelling · Oral ulcerations · Orofacial granulomatosis · Steroid in granulomatous lesions · Ultrasonography

Introduction

Orofacial granulomatosis (OFG) is a chronic inflammatory disorder characterized by persistent or recurrent soft tissue enlargement, oral ulceration, and a variety of other orofacial features. The recurrent chronic orofacial swelling caused by OFG can cause significant cosmetic and

functional problems but can be prevented if the disease is diagnosed early and promptly treated [1].

Case Report

A 28 year old female patient of Asian origin reported to our out-patient department with a chief complaint of a swelling of her upper lip (Fig. 1). She had visited multiple general practitioners for the same complaint but was undiagnosed. History revealed that it started as a small swelling 8 months ago. It steadily grew for 3 months and thereafter remained static. Medical history was non-contributory. On clinical examination it was diffuse, soft, non-tender and non-compressible with no evidence of any sinus or discharge or bruit or pulsations. Routine haematological investigations were performed and were well within normal limits. An ultrasound was performed which showed a mixed echogenic soft tissue swelling of the upper lip with sparsely distributed dilated blood vessels with the peak systolic velocity being 21.86 cm/s in the spectral doppler (Figs. 2, 3). Based on this we arrived at a provisional diagnosis of a vascular lesion of the upper lip. Aspiration was performed but was negative. We proceeded with an incisional biopsy in a hospital set-up. The tissue was obtained from the upper labial mucosa from a para-midline site intra-orally. A deep supra-muscular tissue specimen was obtained and sent for histopathological examination. Microscopically the lesional connective tissue consisted of collagen fibres with spindle shaped fibroblasts with a diffuse chronic inflammatory cell infiltrate composed predominantly of lymphocytes. Focal areas showed the presence of a tubercle consisting of chronic inflammatory cells, Langhan's giant cells and histiocytes. This picture was suggestive of a chronic granulomatous disease

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Fig. 1 Patient with a diffuse upper lip swelling of 8 months duration

Fig. 2 Ultrasonography of the upper lip showing a mixed echogenic soft tissue swelling with dilated blood vessels

(Fig. 4). Following this, we thoroughly investigated the patient to rule out the listed granulomatous diseases (Table 1). The patient was treated with biweekly intralesional injections of Triamcinolone acetonide (Fig. 5) with the simultaneous application of topical clobetasol propionate (0.05%) for 5 weeks.

Etiopathogenesis and Immunological Basis

The precise cause of OFG is still unknown although several theories have been suggested including infection, genetic predisposition and allergy. Some believe it to be a manifestation of Crohns disease. The etiopathogenesis of these

Fig. 3 Spectral doppler of the upper lip

specific granulomas has not been ascertained although many studies throw light on specific features. In a study by Lim et al. [2], the molecular analysis of OFG revealed that local, restricted TCRV β gene usage and clonal T-cell expansion was observed, although the exact biological role of T-cells was uncertain. It was concluded that local cytokine release may be responsible for the non-specific granulomas. Cytokine production by the lymphocytic clone could be responsible for the formation of granulomas in these lesions [3]. Elevated IgG antibody titers directed to 65 kDa mycobacterial stress protein have been identified in a few patients diagnosed with OFG which probably indicates an infectious etiology. Researchers have identified a monoclonal lymphocytic expansion in OFG lesions and have suggested it could be secondary to chronic antigenic stimulation [2].

Discussion

Introduced by Wiesenfeld in 1985, OFG is used to describe diseases which have a variety of clinical presentations, but have a similar histopathological picture of non-specific, non-caseating granulomatous inflammation. OFG includes Melkersson–Rosenthal syndrome (MRS) and cheilitis granulomatosa (CG) of Miescher [4]. Occasionally a typical histopathological picture may not be evident with an absence of non-caseating granulomas [5]. At such times, OFG has been thought to be a diagnosis of exclusion [6].

The clinical presentation of OFG is variable. The most frequent presentation is a non-tender, persistent swelling involving one or both the lips. The lips are most commonly involved and demonstrate a non-tender, persistent swelling [7]. When the swelling is restricted to one or both lips, as in our case, cheilitis granulomatosa may be thought of. With the presence of an associated scrotal tongue, with or

Fig. 4 Photomicrograph at 20× magnification demonstrating non caseating granulomas with the arrow pointing at a Langhans giant cell

Table 1 Tests performed to exclude related granulomatous diseases

Test performed	Results
Complete blood count	Normal
ESR	Normal
Serum ACE levels	Normal
IgE	Normal
Tuberculin skin test	Negative
GI Endoscopy	Normal
Incisional biopsy	Multiple non-caseating granulomas with Langhans giant cells and lymphocytes with acanthosis
	Negative for AFB and PAS reaction

ESR Erythrocyte sedimentation rate, *ACE* angiotensin converting enzyme, *GI* gastro-intestinal, *AFB* acid fast bacilli, *PAS* periodic acid-Schiff

without facial palsy, the diagnosis proceeds towards Melkersson–Rosenthal syndrome [1]. Other findings include cobblestoning, gingival enlargement, fissuring, mucosal tags and ulcerations [8]. The differential diagnosis includes contact allergy, Crohns disease, sarcoidosis, tuberculosis, deep fungal infection and a foreign body reaction. These diseases should be ruled out with a series of thorough investigations before a diagnosis of OFG is given (Table 1).

Investigations are performed to exclude diseases with a similar clinical picture rather than definitively point towards OFG. Ultrasonography was used as an adjunct for diagnosis in the present case. It can be a preferred

Fig. 5 Intralesional injection of Triamcinolone acetonide

adjunctive investigative tool in such swellings as it is non-invasive, non-expensive, does not use ionizing radiation and may be performed as a chair side investigation where available. In this case, we found that OFG mimicked a vascular lesion. The presence of dilated blood and lymph vessels is a universal feature in granulomatous swellings, though not pathognomonic but may serve as a pointer directing towards the diagnosis. Al Johani et al. [8] in their study on OFG in a series of 37 patients found dilated blood vessels and lymphatics in all the cases. The mixed-echogenicity in this ultrasound scan may be a representation of the fibrous connective tissue, inter and intra-cellular edematous changes and the granulomas that form in response to the chronic nature of the disease process.

The granulomas are usually small, loose, and poorly defined consisting of epithelioid histiocytes surrounded by lymphocytes. Multinucleate giant cells are present which can be of Langhans type. Features of edema of the corium with dilated lymphatic and blood vessels and nonspecific inflammatory infiltrate is exclusively present in all cases of OFG [8]. In the present case the connective tissue component was fibrovascular with dilated blood and lymph vessels, which correlates with the ultrasonography findings.

Al Johani et al. [8] from their study suggested a therapeutic ladder based on the severity of the swelling. Mild swellings were to be treated with topically applied steroids or immunosuppressants, moderate and severe swellings were to be treated with a combination of intralesional and systemic steroids as a first line of treatment. Keeping this in mind, we categorized our patient into a swelling of moderate severity and used a combination of topical and intralesional steroids. We postponed the use of systemic steroids, to avoid its adverse effects. Treatment protocol as suggested by El Hakim and Chauvin [9] was followed where the lip was divided into 4 parts and injected with 0.1 ml of Triamcinolone acetonide (10 mg/ml) on a weekly

Fig. 6 Patient at 6 week follow-up

basis. We also suggest the use of lidocaine without epinephrine (1 part) with the intralesional steroid (1 part). We found that it improved patient compliance significantly. Other treatment modalities which have been tried with variable success include hydroxychloroquine, antihistamines [10] and antimicrobials [11–13]. In this case, significant response to therapy in terms of reduction in size of the lip swelling was observed in the second week. Complete resolution was observed at the end of 5 weeks of therapy (Fig. 6), after which the patient was followed up for a year, during which no recurrence was observed.

Conclusions

Orofacial granulomatosis remains a disease with a wide spectrum of presentations. With increasing reports regarding this entity, it should be considered as one of the differentials in diagnosing facial swellings. As in our case, it poses a significant psychological problem to the patient due to facial disfigurement. The fact that the swelling remained undiagnosed for almost 8 months indicates that

familiarity with this pathology is limited. The presented report also highlights the application of ultrasonography as an aid in diagnosis.

Conflict of interest The authors declare no conflict of interest.

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