CASE REPORT

Recurrent lip swelling: a diagnostic challenge

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SUMMARY

A Caucasian woman in her late 20s was referred to the allergy/chest clinic by her general practitioner with an 8-month history of recurrent facial angio-oedema. She had no history of urticaria or airways symptoms and denied any similar problems previously. She had no family history of similar illness and was not on any regular medications. There was no history of atopy. Initially, a clinical diagnosis of idiopathic angio-oedema was made. Despite being treated with several antihistamines with doses equivalent to 40 mg of cetirizine/day, her problem had failed to respond satisfactorily. Later on, she also revealed history of intermittent gastrointestinal symptoms such as abdominal pain and diarrhoea. Routine investigations were unremarkable. The patient was referred to a dermatology clinic and a diagnosis of orofacial granulomatosis was suggested: a rare granulomatous disease presenting with lip enlargement, which may or may not be associated with Crohn's disease. A biopsy of the oral mucosa was consistent with this diagnosis.

BACKGROUND

Orofacial granulomatosis (OFG) is an uncommon condition. The presentation can be similar to other causes of angio-oedema affecting the lips. The condition brings aspects of dermatology, gastroenterology, oral medicine and allergy together. It has therefore been a diagnostic challenge in a young patient in whom the condition has significantly affected her quality of life and antihistamines have been ineffective. Knowledge of the condition may aid other physicians in making the diagnosis, should they come across this in future, thereby allowing appropriate management and observation of related conditions such as Crohn's disease. Early diagnosis and prompt management of OFG would have a significant effect on the long-term prognosis of the condition and reduce morbidity.

CASE PRESENTATION

A Caucasian woman in her late 20s was referred to the allergy/chest clinic by her general practitioner with an 8-month history of recurrent episodic lip swelling, mainly affecting both lips but occasionally associated with periorbital oedema. The episodes initially occurred weekly but gradually became more frequent, lasted longer and were sometimes associated with throat tightness and dysphagia. Eventually, the patient's lips did not fully return to normal and were persistently swollen, causing emotional and mental distress. Initial clinic visits revealed no significant abnormalities of the lips and later visits revealed there was evidence of persistent lip swelling, oral cobble-stoning and mucosal tags,

which are hallmarks of OFG (figures 1 and 2). Her medical history was unremarkable, with no associated atopy or urticaria. There was no significant family or drug history and there were no obvious identifiable triggers. The patient was initially treated with fexofenadine 180 mg once daily with no improvement. Later on, levocetirizine at a higher dose of 10 mg twice daily provided some improvement but the patient still had recurrent lip swelling. Short course prednisolone therapy proved the most effective in reducing the lip swelling, although the patient's facial features never fully returned to normal. With no obvious trigger identified, no improvement with higher dose of antihistamines and the persistent nature of the problem, the rarer causes of chronic angio-oedema were investigated. On further questioning, the patient also reported intermittent abdominal pain and diarrhoea for a few years.

INVESTIGATIONS

Allergy skin prick tests were negative to common allergens and a wide range of food allergens. C1-esterase, functional C1 assay, C3, C4, IgE and IgG subclasses were normal. Thyroid function and an autoimmune profile were normal. A coeliac screen was negative. Routine blood tests revealed low vitamin D (58 nmol/L) and iron levels (6 µmol/L), which were subsequently supplemented by the patient's general practitioner.

The patient was referred to a dermatologist, gastroenterologist and oral medicine specialist for further investigation. A lip biopsy was carried out by the specialist in oral medicine and revealed hyperkeratosis, dilated lymphatic vessels in the superficial cornium and scattered chronic inflammatory cells, which are features seen in OFG. However, the typical appearance of OFG, that is, intramucosal granulomas, was not reported. Features of hyperkeratosis and prominent

Figure 1 Lip swelling in orofacial granulomatosis.

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Figure 2 Lip swelling and ulceration in orofacial granulomatosis.

lymphatic vessels, which are very suggestive of OFG, are shown in figures 3–5.

DIFFERENTIAL DIAGNOSIS

Chronic idiopathic angio-oedema is characterised by intermittent and short lived swelling lasting beyond 6 weeks. In some cases, it may be associated with urticaria. Treatment with antihistamines (sometimes requiring higher doses) is usually effective; however, in this patient there was no improvement with fexofenadine 180 mg once daily or levocetirizine 10 mg twice daily, raising the possibility of other conditions including OFG.

Recurrent angio-oedema may be caused by a number of drugs. ACE inhibitors account for up to 8% of cases.¹ Swelling may start months or even years after first starting the medication, so this is an important consideration. Non-steroidal anti-inflammatory drug (NSAID) use can also cause angio-oedema as a side effect. The patient was not taking any regular medication and was advised to avoid NSAIDs. Hereditary angio-oedema seemed a very likely differential in this patient. It is characterised by low levels of C1-esterase inhibitor due to a defective gene on chromosome 11.¹ Although there was no family history of angio-oedema, there have been reports of spontaneous mutations. However, levels of C1-esterase inhibitor were normal in this patient, excluding this diagnosis. Similarly, a low C4 with paraproteinaemia could have indicated an acquired C1-esterase inhibitor deficiency associated with autoantibodies, but was normal here.²

An important factor in this patient was that there was no identifiable trigger, symptoms were becoming more persistent, did not respond to antihistamines and there were associated abdominal symptoms. Investigations carried out by the gastroenterology department were unremarkable with a negative faecal calprotectin test. It is therefore unlikely that the patient

Figure 3 Lip biopsy showing hyperkeratosis and prominent lymphatic vessels.

Figure 4 Lip biopsy showing hyperkeratosis and prominent lymphatic vessels.

has Crohn's disease. Other granulomatous diseases such as tuberculosis and sarcoidosis are also potential differential diagnoses that may need to be investigated and have already been excluded in this case.

TREATMENT

Unfortunately there is no curative treatment for OFG. Research is limited by the rarity of this condition and only a limited number of publications are available. Some treatments have been attempted with varying degrees of success.

Campbell *et al.*¹ in a limited study, suggest that there may be an allergic component, as benzoate-free, chocolate-free and cinnamon-free diets may be effective, but this is difficult to sustain in the long term.¹ Foods containing benzoates are many and include beer, carbonated drinks, ready meals and most spicy foods. Therefore, there are practical difficulties in keeping a diet free of these food items.

Oral prednisolone is one of the therapeutic measures reported to work well in this condition.³ However, long-term systemic steroids are not ideal due to their side effect profile. In patients who may have oral ulcers or gingival involvement, topical steroids may be of use. Multiple intralesional cortisone injections may also be helpful in the treatment of the condition.³ Immunosuppression such as hydroxychloroquine in addition to steroids, or as steroid-sparing agents may be useful in some

Figure 5 Lip biopsy showing hyperkeratosis and prominent lymphatic vessels.

patients to control the disease.^{3 4} In addition, the antitumour necrosis factor α agent, infliximab has been used successfully³ in selected cases.

Although the mechanism of action is unknown, in a case report, oral antibiotics such as tetracyclines have also been shown to reduce some swelling.² Overall, no formal long-term clinical trials have been conducted to determine the prognosis and the effect of drugs in this condition.

OUTCOME AND FOLLOW-UP

Our patient has had some relief of the facial swelling with an exclusion diet suggested by a nutritionist, which consisted of dairy, grain and salicylaldehyde avoidance. She has also been started on probiotics and nutrient supplements, along with supplementation of vitamin D and iron. Currently, she is being followed up by the oral medicine department. Following the result of her lip biopsy, she had her first intralesional triamcinolone injection of her lower lip. Two weeks after this, her lower lip returned back to normal. She will be returning for further courses of steroid injections and is very pleased with the outcome.

DISCUSSION

OFG is a rare condition associated with all ages and races. It was first described in 1985 by Weisenfeld as “the specific histology 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.”⁵ The granulomas are non-caseating and lymphoedema is also seen.⁶ The cause is unknown; however, there are theories about a genetic predisposition, infection and allergic triggers such as cinnamon, benzoates and even chocolate. Studies have shown that this condition could be an early manifestation of Crohn’s disease but there is no consensus on whether this is the underlying cause.³ Of note, a study has shown that patients with this condition in Spain do not seem to develop Crohn’s disease.⁶ To add to the diagnostic challenge, similar symptoms can be seen in other granulomatous conditions such as tuberculosis and sarcoidosis.

There have been reports of some patients developing Crohn’s disease 5–10 years after orofacial symptom development. Therefore, it is important that patients with OFG are regularly reviewed for new onset gastroenterological symptoms.

The treatment and prognosis remains uncertain at present as there are no randomised controlled trials to determine the long-term outcome of this condition.

Learning points

- ▶ Patients with idiopathic chronic angio-oedema, particularly with visible changes in the lips, who do not respond to conventional therapy, should be investigated for rarer causes including granulomatous diseases.
- ▶ In patients presenting with angio-oedema of the lips, clinicians should examine the lips looking for changes that are suggestive of orofacial granulomatosis.
- ▶ Any patient presenting with recurrent and persistent angio-oedema, oral ulcers and lip changes and/or bowel symptoms should be investigated for associated gastrointestinal conditions such as Crohn’s disease, and should have orofacial granulomatosis excluded.

Competing interests None.

Patient consent Obtained.

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