The Journal of Laryngology & Otology
May 2002, Vol. **116,** pp. 386–388

Melkersson-Rosenthal syndrome

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Abstract
Melkersson-Rosenthal syndrome (MRS) is a rare idiopathic non-caseating granulomatous condition. It is rarely described in otorhinolaryngology-related journals, although facial palsy, lip-swelling, and lingua plicata, are its most common presenting features. This classical triad however is not always present in MRS. Other forms of orofacial swelling exist. This paper describes a patient with a variant of MRS, treated by us with intra-lesional steroid injection. We also discuss the other differential diagnoses that may mimic MRS.

Key words: Melkersson-Rosenthal Syndrome

Introduction

Melkersson-Rosenthal syndrome (MRS) is an idiopathic non-caseating granulomatous condition characterized by facial palsy, lip oedema, and lingua plicata (scrotal tongue or fissured tongue). This classical triad is, however, not always pesent.[1–3] Lip swelling alone (also called cheilitis granulomatosa Miescher) is one of its most common presentations, and may represent a mono-symptomatic form of MRS.[1] Ocular oedema may also present along with MRS, illustrating variations in its presentation.[4] Other facial swellings have also been described, and for this reason, idiopathic orofacial granulomatosis is indicative of MRS. Table I summarizes the features of MRS.

Histological findings of non-caseating epithelioid cell granulomas, multinucleate Langerhan-type giant cells, mononuclear infiltration and fibrosis from affected tissue support the diagnosis of MRS, in the absence of other known causes of granulomatous diseases. These classical features can be difficult to identify, and their absence does not exclude the diagnosis. As MRS is a clinical syndrome, definitive histological evidence is not necessary.[5,6]

Unfortunately, the aetiology or the mechanism of the disease is still not known. There is an endless list of associations (see Table I). History of previous herpes simplex facial infection may be an aetiological factor. Associations with previous odentogenic infection,[3] adeno-tonsillar infection, and *Mycobacterium tuberculosis*,[7] suggest a possible bacterial origin for MRS. Abnormal TCRV gene usage by lesional T lymphocytes and clonal T-cell expansion within the granuloma may also have a role.[8] Horstein considered MRS as a neuro-mucocutaneous disorder and he speculated a possible micro-neurovascular involvement.[1]

The treatment of MRS is arbitrary and based on anecdote. Various therapeutic options (see Table I) have not produced consistent results. One study quoted a remission rate of 50 per cent and 60–75 per cent of patients suffered recurrence.[9] Identification and eradication of any odontogenic infection may be beneficial.[3] Surgical cheiloplasty offers cosmetic correction for severe cases, although disease can still recur. The poor results and various treatment modalities reflect our lack of understanding of the MRS, and the recurrent progressive nature of the condition.

Case report

A 21-year-old female had presented two years ago with three episodes of recurrent swellings of her lips (see Figure 1). Her immunological screens, and upper limb nerve conduction studies were normal and no causes could be identified. Apart from a previous adeno-tonsillectomy as a child, she had a clear medical history. A diagnosis of monosymptomatic MRS was made. No tissue biopsy was taken for fear of causing further deformity to her face.

Her lip swellings however, did not respond satisfactorily to medical therapy, including clofazimine, dapsone, metronidazole, systemic steroids, and tacrolimus. She received three doses of intra-lesional steroid injections to her lips under local anaesthetic. On each occasion, her lips swelling responded (see Figure 2).

Discussion

From the ENT perspective, an awareness of MRS is important as the condition can present with facial palsy and orofacial swelling. Lingual plicata is relatively common. Its prevalence in two to five per cent of the population questions its association with MRS.[1,10]

Bell's palsy (idiopathic facial palsy) however is the most common cause of a VIIth cranial nerve lesion; followed by trauma, tumours, herpes zoster oticus, ear infection, parotid malignancy and a long list of other causes. Bell's palsy is usually self-limiting, and spontaneously remits in up to 85 per cent of the patients.[11] Bell's palsy can also recur, thus mimicking MRS. Other unusual causes of facial palsies should not forgotten. They include: Lyme disease (borreliosis), human immunodeficiency virus (HIV) infection, human T-cell leukaemia virus type I (HTLV 1) infection, trauma, and Ramsay-Hunt syndrome.[12]

Orofacial swelling is the most common presentation of MRS (80–100 per cent).[6,10] The upper lip is most frequently affected, followed by the lower lip, buccal

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Accepted for publication: 8 November 2001.

TABLE I
SUMMARY OF MELKERSSON-ROSENTHAL SYNDROME

Incidence:	0.08% of general population
Sex ratio:	Reports of equal male and female ratios, and others of a female predominance
Age group:	20–30 years old
Major symptoms:	Orofacial swelling – upper lip (most frequently); usually non-specific, asymmetrical – cheek – lower lip – nose – eyelids – upper alveolar processes Facial palsy Lingua plicata
Other symptoms:	Trigeminal neuralgia and other cranial nerve symptoms Migraine Otosclerosis Raynaud's phenomenon Blurred vision Hyperplastic gingivitis Buccal and palatal enlargement Salivary gland dysfunction Sweat glands dysfunction
Associations	Familial Genetic – autosomal dorminant ? chromosome 9p11 Crohn's disease Crohn's disease Allergy Angio-oedema Herpes simplex virus infection Adenoid and tonsillar infection Odontogenic infection Streptococcus C infection *Mycobacterium tuberculosis* Leprosy Candidiasis Menstrual cycle
Investigations:	Largely guided by history and examination. There is no specific test for MRS. Histological sampling is not necessary. Even when histology is available, the absence of classical MRS features does not exclude its diagnosis. FBC, U and E, CRP, immunological screens, C1-esterase, serum ACE, audiogram, CXR, radiological imaging will help to identify other differential diagnoses.
Histology	Non-caseating epithelioid cell granulomas + multinucleate Langerhan-type giant cells Mononuclear infiltration and fibrosis Non-specific inflammation
Treatment	*Most therapeutic options produce at best short term benefits; recurrence is common* Corticosteroid (oral and intralesional) Immunosuppressants (azathioprine, cyclosporin A) Antibiotics (penicillin, tetracycline, erythromycin, clindamycin, metronidazole) Antihistamines (terfenadine, diphenhydramine) Danazol Hydrochloroquine Antilepromatous agent (clofazimine) Eradication of underlying odontogenic infection Facial physiotherapy Surgery is not commonly used due to the tendency of the disease to recur

FBC: full blood count, U and E: urea and electrolytes, CRP: C reactive protein, ACE: angiotensin converting enzyme, CXR: chest radiograph.
Compiled from references 3, 4, 6, 17, 18, 19, 20, 21, 22

mucosa, palate, the periorbital swelling. Angio-oedema, associated with potential airway obstruction, can present as orofacial swelling. Complement levels and C1 esterase inhibitor levels should be measured in this group of patients, as congenital angio-oedema does not respond to antihistamines, adrenaline, and corticosteroids. Congenital angio-oedema responds to danazol, and in an emergency, a course of C1 esterase inhibitor may be life-saving.[13] Both forms of angio-oedema may recur, the hence mimic MRS. During the evaluation of orofacial swelling, sarcoidosis should be considered in the differential diagnosis, as it shares similar histology of non-caseating granulomas with MRS.[14] It differs from MRS as it is a steroid responsive and self-limiting condition, associated with hilar lymphadenopathy, hypercalcaemia, positive Kveim test and raised angiotensin-converting enzyme (ACE) levels. Other differential diagnoses for orofacial swelling include: hypothyroidism, superior vena cava obstruction, recurrent erysipelas, amyloidosis, lymphangioma, lymphoma, eosinophilia, chronic herpes simplex labialis, leprosy, Ascher's syndrome (characterized by upper lip swelling, blepharochalasis, accessory lacrimal gland inflammation and thyromegaly), and Crohn's disease.[14] There are speculative reports that oral granulatomosis may represent oral

https://doi.org/10.1258/0022215021910861 Published online by Cambridge University Press

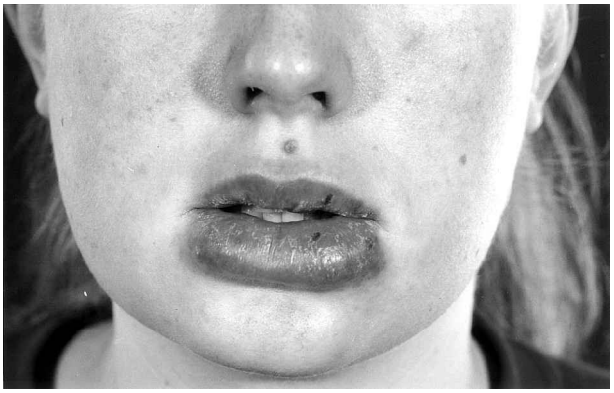

FIG. 1

Painless erythematous swelling of the lips, one of the most common presenting signs of Melkersson-Rosenthal syndrome.

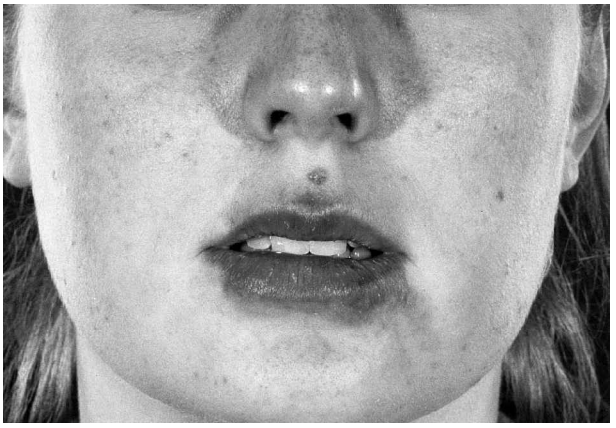

FIG. 2

A reduction in lip swelling one year after injection with subdermal triamcinolone.

Crohn's disease, but the evidence is not conclusive at present.[15,16] Recurrent, painless orofacial swelling appears to be unique to MRS.[6]

This case of monosymptomatic MRS illustrates the lack of long-term success of most medical therapies for this condition. Intra-lesional steroids have produced short-term improvement in her swollen lips. Its natural history is difficult to predict but it frequently has a chronic progressive course, and facial palsy is not uncommon. So far, there are no reports of malignant changes associated with MRS/orofacial granulatomatosis.

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Professor N. S. Jones takes responsibility for the integrity of the content of the paper.
Competing interests: None declared