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# Melkersson-Rosenthal syndrome as a differential diagnosis of lip swelling

*Síndrome de Melkersson-Rosenthal como diagnóstico diferencial de edema labial*

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**ABSTRACT**

Melkersson-Rosenthal syndrome is a rare condition characterized by the classic triad: orofacial edema, fissured tongue, and facial paralysis. Only 1 or 2 manifestations of the triad may be present for a prolonged time, making diagnosis difficult. It is called Miescher's cheilitis when the only manifestation is orofacial edema, with characteristic histology. The present report aims to alert to the diagnosis of Melkersson-Rosenthal syndrome in cases of chronic lip angioedema, with a review of the literature. A 40-year-old woman presented with lip swelling since the age of 23, with no regression of the swelling for 5 years, without pruritus or triggers. A fissured tongue was observed on physical examination. Complementary tests showed no abnormalities. Persistent orofacial edema, fissured tongue, lower lip biopsy showing chronic cheilitis (hyperkeratosis and perivascular lymphocytic infiltration) and the exclusion of differential diagnoses through complementary tests led to the diagnosis of Melkersson-Rosenthal syndrome. The patient was then referred to the Plastic Surgery Service, which recommended surgical removal of excess lip tissue. The diagnosis of the syndrome is essentially clinical. Treatment should be individualized, aiming to alleviate the clinical manifestations in each case. Multidisciplinary follow-up is important to minimize psychological damage and improve prognosis. Melkersson-Rosenthal syndrome can present as chronic lip angioedema and fissured tongue, without facial paralysis, which may delay the diagnosis, as in the present case. It is necessary to consider the syndrome to allow earlier diagnosis and management and to provide a better quality of life for these patients.

**Keywords:** Allergy and Immunology, angioedema, Melkersson-Rosenthal syndrome, facial paralysis.

**RESUMO**

A síndrome de Melkersson-Rosenthal é uma condição rara caracterizada pela tríade clássica: edema orofacial, língua fissurada e paralisia facial. Pode haver apenas uma ou duas manifestações por tempo prolongado, dificultando o diagnóstico. É denominada queilite de Miescher quando a única manifestação é o edema orofacial, com histologia característica. O presente relato tem como objetivo alertar para o diagnóstico da síndrome de Melkersson-Rosenthal em casos de angioedema labial crônico, com revisão da literatura. Mulher de 40 anos apresentando edema labial desde os 23 anos de idade, sem regressão há cinco anos, sem prurido, sem desencadeantes. Observou-se língua fissurada ao exame físico. Sem alterações aos exames complementares. O edema orofacial persistente, a língua fissurada, a biópsia de lábio inferior evidenciando queilite crônica (hiperqueratose e infiltração linfocítica perivascular) e a exclusão de diagnósticos diferenciais através de exames complementares permitiram o diagnóstico da síndrome de Melkersson-Rosenthal. A paciente foi então encaminhada à Cirurgia Plástica, que orientou retirada cirúrgica do excesso labial. O diagnóstico da síndrome é essencialmente clínico. O tratamento deve ser individualizado, visando o alívio das manifestações clínicas apresentadas em cada caso. É importante o acompanhamento multiprofissional tentando minimizar danos psicológicos e melhorar o prognóstico. A síndrome de Melkersson-Rosenthal pode apresentar-se como angioedema labial crônico e língua fissurada, sem paralisia facial, podendo retardar o diagnóstico, como no presente caso. É necessária a lembrança da síndrome para o diagnóstico e conduta mais precoce, para melhor qualidade de vida destes pacientes.

**Descritores:** Síndrome de Melkersson-Rosenthal, angioedema, paralisia facial, alergia e imunologia.

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## Introduction

Lip swelling is a common complaint in the physician's office and is a symptom of several diseases, allergic or not. Researching the causes of orofacial edema is important to provide adequate treatment and patient guidance.

Melkersson-Rosenthal syndrome (MRS) was initially described in 1928 as facial edema by Melkersson. In 1931, Rosenthal added lingua plicata to the list of symptoms. In 1949, the syndrome was considered a neuromucocutaneous disorder characterized by a classic triad of orofacial edema, lingua plicata, and facial palsy.[1,2] Only 1 or 2 manifestations may be present for a prolonged time, making it difficult to diagnose this condition. The presence of orofacial edema alone, with characteristic histology, characterizes Miescher's granulomatous cheilitis.[2] The pathogenesis of MRS is still poorly understood, but it is believed to be multifactorial, involving allergic, infectious, autoimmune, and hereditary causes.[3-6]

The objective of this study was to report the case of a patient diagnosed with MRS after 17 years of severe lip swelling and conduct a literature review to warn about the possible diagnosis of this condition.

This retrospective, clinical and laboratory, longitudinal study of medical records was conducted after the patient provided written informed consent. A literature review was conducted on MEDLINE/PubMed, Biblioteca Virtual em Saúde, and Google Scholar databases.

## Case report

A 40-year-old female seamstress complained of lip swelling since she was 23 years old. The swelling would appear suddenly, usually every 4 months, with periods of complete remission in between. She reported having sought health services several times and being treated with oral corticosteroids, nonsteroidal anti-inflammatory drugs, and antihistamines on separate occasions, but without improvement of the condition. The episodes became more frequent, longer, and did not respond to treatment. The patient reported being discouraged by treatment failure and swelling recurrence and completely discontinued the treatment initially proposed. After pregnancy, the episodes of lip swelling became more frequent and, eventually, persistent.

She was referred to a specialized sector of a teaching hospital, where she complained of swelling in the upper and lower lips for 17 years, with no remission in the past 5 years (Figure 1). She denied the presence of urticaria, pruritus, fever, triggering factors or other complaints, as well as previous comorbidities or family history of swelling. On physical examination, she showed marked and asymmetric swelling of the lower and upper lips, with preserved sensitivity and no local hyperemia. In addition to labial angioedema, the examination revealed several fissures on the dorsum of the tongue that were attached to a central fissure, which the patient had never mentioned.

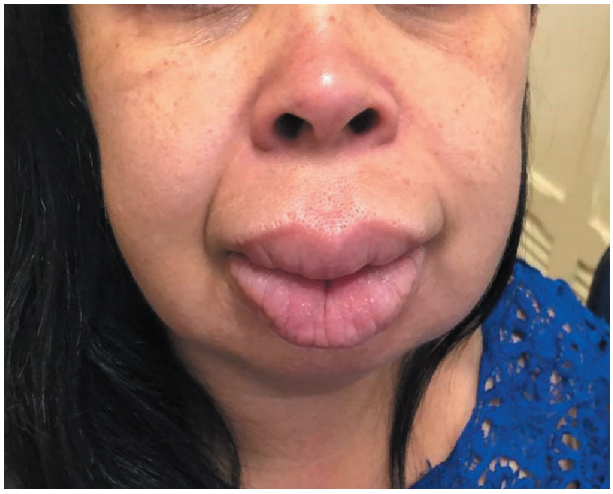

**Figure 1**
Patient with upper and lower lip swelling for 17 years: the most frequent form of Melkersson-Rosenthal Syndrome

Based on patient history and physical examination, the following diagnostic hypotheses were raised: MRS, hereditary angioedema, acquired angioedema, and adverse reaction to nonsteroidal anti-inflammatory drugs. The following laboratory tests were requested: CH50 320 U (reference range [RR] = 170-330), C3 147 mg/dL (RR = 67-149), C4 38 mg/dL (RR = 10-38), quantitative (16 mg/dL) and functional C1-esterase inhibitor (C1-INH) within the normal range (RR = 14-30), normal complete blood count, and absence of autoantibodies.

Lower lip biopsy showed hyperkeratosis, swelling, and mild perivascular lymphocytic infiltration, which characterize chronic cheilitis. Local infiltration with corticosteroids and use of dapsone were

recommended. The patient received a few applications and used the oral medication for 2 months irregularly. Due to treatment nonadherence and lack of improvement, she stopped attending medical appointments. She returned for follow-up 2 years later with permanent lip swelling, as well as weight loss, lack of appetite, and marked psychosocial impairment, with emotional lability and total social isolation.

The patient was referred to the plastic surgery department to evaluate the possibility of surgical correction to improve her quality of life. After evaluation, surgical removal of excess tissue was recommended, and the patient appeared to be motivated. She is currently in preoperative evaluation, awaiting the procedure.

## Discussion

The patient only complained of lip swelling for 17 years. After lingua plicata was identified on clinical examination, the hypothesis of MRS was raised, and laboratory tests were requested to complement the investigation. The diagnosis of MRS is essentially clinical and based on the presence of 2 manifestations of the classic triad.[5] Cases that only present with orofacial edema require biopsy for the diagnostic confirmation of cheilitis, which is the most frequent monosymptomatic form of the syndrome, called Miescher's granulomatous cheilitis.[2-6]

The onset of MRS is more common in young adults, between the second and third decades of life,[3] as in the present case. It has an estimated incidence of 0.08% in the general population, but the number of cases is believed to be underreported.[4] MRS mostly affects women, but there are no differences between ethnicities.[3] The classic triad of orofacial edema, facial palsy, and lingua plicata is observed in only 8% to 25% of cases.[2,7]

In this syndrome, orofacial edema is painless, asymmetrical, nonpruritic, non-erythematous, and may affect the lip, gums, tongue, chin, cheeks, and even the periorbital region, with the upper lip being the most frequently affected part.[6,8] The swelling regresses rapidly in most cases. However, increased swelling recurrence decreases the chances of regression, and the swelling may become permanent, as in the present case.

Lingua plicata is a nonspecific sign observed in 20% to 77% of cases.[9] The fissures appear along the entire dorsal surface of the tongue and are attached to a single central fissure, as in the present case. Although bacterial and fungal infections are commonly associated with lingua plicata, the patient had no signs of infection.[9]

Peripheral facial nerve palsy in RMS is recurrent, of sudden onset, uni or bilateral, and is observed in 90% of cases,[8] with no difference between genders. It may occur alone years before or after orofacial edema, thus the diagnosis should be revised according to the evolution of the condition. Although the classic triad is well defined, signs and symptoms that suggest the involvement of other cranial nerves may be included in the diagnostic criteria: changes in ocular motility and functionality of salivary and lacrimal glands, hyperacusis, hyperhidrosis, and hypergeusia, as well as different ocular manifestations such as retrobulbar neuritis and blepharochalasis.[8] The patient in question did not have facial palsy or cranial nerve involvement during the 17 years of illness, which may have delayed the diagnosis.

Additional tests are required to exclude differential diagnoses such as hereditary angioedema, foreign body reaction, sarcoidosis, Crohn's disease, Wegener's vasculitis, amyloidosis, infections, Bell's palsy, orofacial herpes, contact dermatitis, and allergic reactions.[5,6] The patient in question showed no signs of infection. Autoimmune diseases, which may co-occur with MRS, were ruled out due to the absence of manifestations and autoreactive antibodies. The hypothesis of hereditary angioedema was ruled out by laboratory tests. Acquired angioedema due to C1-INH deficiency may be caused in particular by autoimmune or lymphoproliferative disorders, which were ruled out by clinical examination and laboratory tests.

Microscopy of MRS angioedema is characterized by a chronic inflammatory process, with noncaseating epithelioid granulomas, surrounding mononuclear infiltrate, Langerhans giant cells, and perivascular lymphoplasmacytic infiltrate.[1-3,5,10] In this report, the biopsy was relevant because it showed hyperkeratosis, edema, and perivascular lymphocytic infiltration, which are characteristic of chronic cheilitis.

The patient's clinical manifestations of recurrent and then persistent lip swelling, lingua plicata, and chronic cheilitis identified by biopsy allowed the diagnosis of MRS, even in the absence of facial palsy.

Anti-inflammatory drugs, especially oral or intralesional corticosteroids, methotrexate, and dapsone[10,12] are among the main treatments for MRS. However, they were unsuccessful in this patient. A surgical approach should be considered in case of deformed swelling with psychosocial impairment,[13,14] as in the present case. Recurrent treatment dropout by the patient shows the direct impact of psychological and emotional changes resulting from the physical appearance of progressive edema.

Given the impact of the diagnosis on quality of life, the need to recognize the clinical manifestations of MRS at an early stage and establish integrated follow-up for a better prognosis is extremely important. In addition to pharmacological therapy, multidisciplinary action involving dermatologists, plastic surgeons, otolaryngologists, physical therapists (in the case of paralysis), and follow-up with psychologists and psychiatrist to prevent psychosocial impairment is required.

## Conclusion

In this case report, the patient had presented lip swelling for 17 years, which was initially recurrent and later became persistent, in addition to the clinical finding of lingua plicata (which was never reported by the patient). She was diagnosed with MRS. Lower lip biopsy showed changes that were consistent with chronic cheilitis, while laboratory tests ruled out differential diagnoses, contributing to the final diagnosis. The lack of facial palsy may have contributed to the late diagnosis, as well as the lack of perception of lingua plicata by the patient.

This report shows the importance of including MRS in the differential diagnosis of recurrent or persistent lip swelling accompanied by lingua plicata, even in the absence of facial palsy. Earlier diagnosis of the syndrome would have provided better quality of life for the patient.

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