CASE REPORT

Melkersson Rosenthal syndrome in a patient with granulomatous cheilitis about a case reported in the General Teaching Hospital of Riobamba as a single clinical manifestation.

Carlos Alberto Martínez Fiallos,* Miriam Arboleda, María Gabriela Martinez A.*****

* *Dermatologist of the General Teaching Hospital of Riobamba.*
** *Nurse at the General Teaching Hospital of Ambato*
*** *Student of Nursing Universidad Técnica de Ambato*

Correspondence: cmartinezfiallos@gmail.com

Key words: granulomatous cheilitis, Melkersson Rosenthal syndrome, labial edema, facial paralysis, fissured tongue

Reception date: 07/01/2023
Acceptance date: 11/05/2023

ABSTRACT

Miescher's granulomatous cheilitis is characterized by the appearance of recurrent labial edema on one or both lips, which may be persistent. It has been considered as a monosymptomatic form of Melkersson Rosenthal syndrome. This syndrome usually occurs with edema either in the upper or lower lip, facial paralysis and fissured tongue. It is an infrequent one, with few cases described, although it may be underdiagnosed due to its lack of knowledge. The diagnosis of granulomatous cheilitis is mostly clinical, although its diagnosis can also be confirmed by histological evaluation. After carrying out its diagnosis, a comprehensive evaluation of the patient should be recommended, in order to rule out the rest of the syndromic associations described in the medical literature.

The clinical case presented is a 20-year-old man with a clinical picture of lower lip edema, asthenia, dizziness and fissured tongue, who had a good clinical evolution and recovery.

We opted for the presentation of the clinical case of Melkersson Rosenthal Syndrome in a patient with granulomatous cheilitis as it is a rare entity with unique clinical characteristics for its diagnosis.

INTRODUCTION

Granulomatous cheilitis (G.Q.) is a chronic, rare, painless, idiopathic inflammation of the lip. It is considered a manifestation of orofacial granulomatosis (OFG), which is a clinical term describing orofacial swelling caused by granulomatous inflammation without emptying in the absence of systemic disease. When accompanied by facial paralysis and pleated tongue, it is known as Melkersson-Rosenthal syndrome.[1]

Melkersson-Rosenthal syndrome manifests as a triad of lip or facial swelling, recurrent partial or complete facial paralysis, and fissured tongue. Miescher's gran-

ulomatous cheilitis is characterized by inflammation restricted to the lips. Some clinicians consider granulomatous cheilitis to be a monosymptomatic form of Melkersson-Rosenthal syndrome. The etiology of this disease is unclear, but the condition has been related to an abnormal immune reaction.[2]

The exact etiology of orofacial granulomatosis is unknown. Usually the normal architecture of the lips is altered by lymphedema and non-caseating granulomas in the lamina propria. Excessive permeability of facial cutaneous vessels as a result of abnormal regulation of the autonomic nervous system has been suggested as a potential cause.[2,3]

The most common identified cause of orofacial granulomatosis is diet or other antigens. Contact antigens such as cobalt, gold, or mercury may also be involved. Hornstein proposed that nonspecific antigens may stimulate perivascular cells to form granulomas, causing vessel obstruction and subsequent facial inflammation.[3]

Several theories have been postulated, including infection, genetic predisposition and allergy. Monoclonal lymphocytic expression, secondary to chronic antigenic stimulation, cytokine production leading to granuloma formation and a cell-mediated hypersensitivity reaction have also been suggested.[2]

Orofacial granulomatosis may also result from reaction to some foods or drugs, particularly cinnamon aldehyde and benzoates, but also butylated hydroxyanisole, dodecyl gallate, menthol and monosodium glutamate. Protease-activated receptor 1 and 2 expression occurs in orofacial granulomatosis.[3]

Within the symptomatology, granulomatous cheilitis is characterized by a firm and recurrent inflammation of one or both lips and is the most common monosymptomatic form of Melkersson Rosenthal Syndrome.[4] Non-caseating CG belongs to the group of orofacial granulomatosis and it has been suggested that it may be a subtype of Crohn's disease and precedes its diagnosis by years, especially in children.[5]

Corticosteroid therapy is a classic treatment can be administered locally, topically or intralesionally, and more rarely, systemic corticosteroid for short treatments such as prednisolone: 0.3 to 0.7 mg / kg / d; 25 to 50 mg / d. Other treatments have also been tried for their anti-inflammatory or immunomodulatory effects, such as topical tacrolimus or oral thalidomide, dapsone and doxycycline, with inconsistent efficacy.[4]

PRESENTATION OF THE CLINICAL CASE

Male, 18 years old, born and resident in Riobamba with no personal clinical or family history of importance, with clinical picture of more or less 2 weeks of evolution that begins with burning pain on the tongue located on the dorsum that increases with the temperature of the food 10 days ago more or less presents ulcerative lesion on the lower lip which is accompanied by edema, Physical examination revealed a dermatosis characterized by the presence of an ulcerated lesion covered by necrotic crust on the vermilion of the lower lip with extension to the transitional epithelium (photo 2).

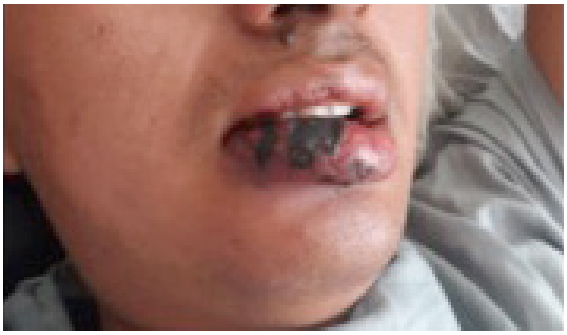

Photo 1: Edema of the lower lip, predominantly on the right portion with deformation of the lower lip.

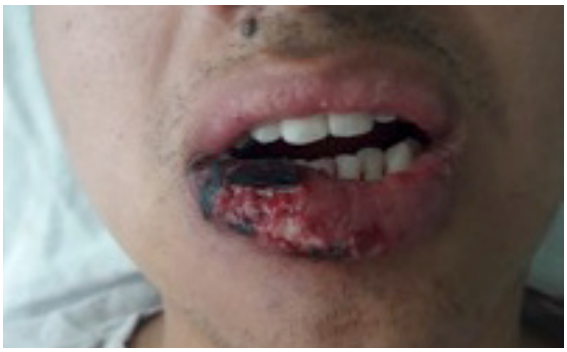

Photo 2: Ulcer of the lower lip with regular edges with a background containing granulation tissue and covered by necrotic crust, extending towards the labial mucosa in its gingival portion.

DISCUSSION

QG is a rare disease of undefined incidence and prevalence. According to Gharbi a study estimated the incidence at 0.08% of the general population.[4] And the reported incidence of Melkersson Rosenthal Syndrome is between 0.2 and 80 in 100,000 per year. According to Savasta this incidence may be underestimated, as this syndrome is misdiagnosed and underestimated, and several authors have reported a mean diagnostic delay of nine years.[6] This disease can have its onset at all ages, however it usually occurs in young adults between the second to fourth decade of life and is rare in childhood.[4,6] Most authors indicate an equal distribution of sex, although some affirm that it is slightly more common in women.[4,7] According to the described incidence, our patient would be within the estimated age range since he is 20 years old.

This entity is a rare disease of unknown etiology, with neuromucocutaneous involvement affecting the orofacial innervation. The observation of familial aggregation and the suggestion of a relationship with autosomal de novo t translation support the hypothesis of a genetic predisposition. An association with infections and autoimmune disorders has also been described.[5,8]

The most common monosymptomatic presentation of the lips is unilateral or bilateral. Lingua plicata is characterized by the development of deep grooves or fissures on the dorsal and lateral surfaces of the tongue which is a benign condition frequently found in healthy people, but is more common in people with Melkersson Rosenthal syndrome, chronic granulomatous disease, psoriasis and Sjögren's syndrome. And finally recurrent facial nerve palsy is less common, clinically indistinguishable from Bell's palsy and may precede granulomatous cheilitis by years. Melkersson Rosenthal syndrome may also be associated with other cranial nerve palsies and dysautonomia.[5]

However, it should be noted that only 8-25% of cases show the complete triad, as most patients present with oligosymptomatic symptoms or monosymptomatic forms. Orofacial edema without recurrent pain, also called Miescher's granulomatous cheilitis, is the most frequent monosymptomatic presentation of Melkersson Rosenthal syndrome, and the diagnosis is suggested by the identification of a non-caseating granuloma in a mucocutaneous biopsy of the subjects. Oligosymptomatic or complete forms do not require additional biopsy for investigation, since Melkersson Rosenthal syndrome is a clinical syndrome.[6]

Generally to reach the diagnosis it is necessary to know the above mentioned clinical forms that this disease presents. Histological examination is not necessary for the diagnosis of the complete form of Melkersson Rosenthal syndrome, which can be easily established based on clinical findings. However, histological analysis is necessary for incomplete forms, especially for the differential diagnosis of sarcoidosis and Crohn's disease.[4]

On physical examination, the earliest manifestation of granulomatous cheilitis is a sudden diffuse or occasionally nodular swelling of the lip or face involving the upper lip, lower lip, both lips, and one or both cheeks. The forehead, eyelids, or one side of the scalp may be involved although it is less common. As mentioned above, a fissured or folded tongue is seen in 20-40% of patients.[3]

Lip edema may feel soft, firm or nodular to palpation. Once chronicity is established, the enlarged lip appears cracked and fissured, with reddish-brown discoloration and scaling. The fissured lip becomes painful and eventually takes on the consistency of a firm gum. The edema may regress very slowly after a few years. Regional lymph nodes are usually minimally enlarged in 50% of patients.[3]

In 30% of patients a facial paralysis of neuromotor type can be observed. This can be uni or bilateral, partial or complete. Other cranial nerves such as the olfactory, auditory, glossopharyngeal, or hypoglossal nerves are also occasionally affected.

Central nervous system involvement has been reported, but the significance of the resulting symptoms is easily

overlooked because they are so variable. Sometimes they mimic multiple sclerosis but often with an ill-defined association of psychiatric and neurological features. Autonomic disturbances may also occur.[3]

Performing a biopsy of the labial mucosa is very useful in the diagnosis. Among the findings we can find: perivascular lymphocytic infiltration with granuloma formation in the submucosa and the deeper areas of the biopsy show the presence of chronic inflammatory infiltration of the salivary glands of the lips.[5]

Some histopathologic features are not constant, and in their absence the diagnosis of granulomatous cheilitis should not be formally excluded. These features may be granulomatous infiltrates consisting of epitheloid cells and multinucleated giant cells, associated with some degree of lymphedema and fibrosis.[4]

The management of granulomatous cheilitis becomes difficult due to the lack of knowledge about its etiology. The goals of treatment are to improve clinical appearance and patient comfort. The proposed symptomatic treatments are simply aimed at avoiding or spacing recurrences, particularly in the edematous stage. The goal of treatment is to relieve these patients and improve their quality of life, often greatly disturbed by the unpleasant and distressing nature of macrocheilitis and orofacial edema. Although rare, spontaneous remission is possible. Elimination of odontogenic infections may reduce inflammation in certain patients.[2,4]

In order to arrive at the cause it is necessary to investigate other factors such as gastrointestinal symptoms, which may raise suspicion of undiagnosed Crohn's disease, as well as to inquire about a chronic parasite, which may indicate sarcoidosis, tuberculosis or histoplasmosis. The physical examination should include a cranial nerve examination to determine facial nerve involvement. A complete oropharyngeal examination specifically looking for poor dentition or malignant lesions, an examination of the tongue for plication to indicate the full form of Melkersson Rosenthal Syndrome. An inspection for aphthous ulcers that may early suggest Crohn's disease, inspection for erythematous lesions suggestive of rosacea, and palpation of the affected lip for pain.[1]

Speaking more deeply about the specific events that happen in lip edema, we have that in granulomatous cheilitis, the normal lip architecture is altered by the presence of lymphedema and nonplatelet-forming granulomas in the lamina propria. TH1 immunocytes produce interleukin 12, RANTES / MIP-1α and granulomas. Protease-activated receptor 1 and 2 expression occurs in orofacial granulomatosis.[7]

According to Bohra who described the pathogenesis of Melkersson Rosenthal syndrome, he suggested that abnormal regulation of the autonomic nervous system leads to excessive permeability of facial cutaneous vessels. From this abnormal circulation, nonspecific antigens stimulate perivascular cells to form granulomas. Obstruction of perivascular vessels by granuloma has been proposed as a causative factor of inflammation.[7]

Given that the patient under study presented certain symptomatology and confirmatory tests, we could deduce that the most likely etiology is infectious. With a leukocytosis of 22,000 and the inflammatory response that occurred in him, which was the fever, we can suspect this cause.

When speaking of the symptomatology of this entity, it is said to present as edema of one or both lips. When granulomatous cheilitis is accompanied by facial muscle paralysis and fissured tongue, it is known as Melkersson-Rosenthal syndrome. However, the classic triad is very rare, representing only 25-40% of cases and the oligosymptomatic and monosymptomatic forms are the most common clinical presentation. The monosymptomatic form is referred to as Miescher's cheilitis.[9,5]

Clinically, the first episode usually subsides within hours or days, but both the frequency and duration of symptoms increase until they become persistent. The disease may also affect other oral and facial regions including the face, oral mucosa, gums, tongue, pharynx,

and larynx. Patients may complain of pain or a burning sensation, especially if the oral region presents with erythema, fissures, erosions, or peeling of the lips. Generally the oral mucosa is thickened and edematous with a lobulated appearance. When palatal involvement is present it has the appearance of a characteristic gingival hyperplasia. When present it has an irregular distribution and a predilection for the anterior region. If other areas of the face are involved, there may be enlargement towards the lymph nodes. The tongue may develop fissures, edema, paresthesias, erosions or taste alterations. Papules or hyperplastic tissue may also be seen on the palate.[10]

In comparison with this case, the most important sign presented by the patient was edema of the lower lip, which did not subside and was accompanied by pain. The pain in the patient appeared due to the appearance of the lip that presented desquamation and erosions due to inflammation. He did not present facial paralysis or fissured tongue so we could say that it was a monosymptomatic form of Melkersson Rosenthal syndrome.

For the diagnosis of this pathology it is necessary to perform a complete clinical history including anamnesis, physical examination and appropriate diagnostic studies. As mentioned in the literature previously, this disease is mostly clinical, therefore it is necessary to properly identify its signs and symptoms. After this, the most accurate confirmatory test is the biopsy of the affected area, in this case the lip.[9,11]

Once the biopsy has been performed we must look for certain features to confirm it. Histologically, the diagnosis is based on the infiltration of lymphocytes, plasma cells and non-caseating granulomas that cluster around scattered blood vessels with giant Langerhans cells and epitheloid cells. Once granuloma formation is documented, special stains are used to rule out other granulomatous diseases.[9,11,12]

The patient under study presented the monosymptomatic form of Melkersson Rosenthal syndrome due to his symptomatology, which was confirmed by biopsy. The biopsy findings in this case were erosions on the epidermal side, ulcerated skin with neutrophilic inflammatory infiltrate, congestive vessels and thickened hyaline bundles which was compatible with granuloma and giant cell formation.

For the treatment of Granulomatous Cheilitis/Melkersson Rosenthal Syndrome intralesional steroids have been reported to provide the most improvement, however, in most patients, there are multiple treatments. Currently, the most commonly agreed upon treatment for patients with isolated granulomatous cheilitis is intralesional. Triamcinolone injections although it is not uncommon for the benefit to be short-lived, requiring additional treatments. Systemic corticosteroids have often been used with moderate success, but long-term side effects make this treatment option less used. Other agents with anti-inflammatory properties have also been used which may offer a better side effect profile when used for long-term suppressive therapy. These include clofazimine, dapsone, sulfapyridine, danazol, hydroxychloroquine and antibiotics such as doxycycline and metronidazole. Success with other treatments has been reported anecdotally, including intralesional pingyangmycin plus dexamethasone.[3,11,12]

It is important to mention that simple compression for several hours daily can produce sustained improvement. Compression devices can be used overnight to reduce lip edema. And in situations where medical therapy fails or in extremely disfiguring cases of Granulomatous Cheilitis and Melkersson Rosenthal Syndrome, surgical cheiloplasty is performed to reduce lip size and improve cosmetic appearance.[3,12]

Due to the absence of a precise diagnosis at the beginning, the patient received several different treatments without improvement. However, once assessed by the Dermatology specialty, treatment with corticosteroids and antibiotics was decided. In this case, Dexamethasone 8mg, Clindamycin initially intravenously and then orally, and Metronidazole 500mg orally were used. This indicates a good therapeutic option according to the literature consultation (photo 3).

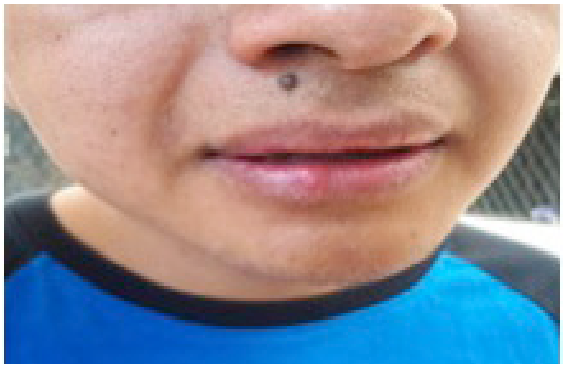

Photo 3: After 10 days of treatment with corticosteroids at 1/mg/kg per day, complete resolution of the inflammatory process.

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Histopathology

SERVICIO:	SALA:	CAMA:	C. EXTERNA:	EDAD:	SEXO:	FECHA:
GINECO		44		20 años	M	29-11-2018

Diagnostico Clínico: Queilitis granulomatosa.
Operación Practicada:
Tratamiento:
Origen y naturaleza de la muestra: Piel de labio inferior. ATIBA
Datos de orientación diagnóstica:

SOLICITANTE:	NUMERO DE INFORME:
Dr.	3251-2018

MACROSCOPIA:

Se recibe elipse de piel que mide 0,7 x 0,5 x 0, 2 cm, la cara epidérmica es grisácea con áreas de erosión, el extremo opuesto es cruento. Se procesa toda la muestra: 1 casete.

MICROSCOPIA:

Los cortes muestran piel ulcerada con importante infiltrado inflamatorio neutrofílico, vasos sanguíneos congestivos y haces hialinos engrosados.

DIAGNOSTICO:

- **BIOPSIA DE PIEL DE LABIO INFERIOR:**
  -DERMATITIS NEUTROFILICA PERIORAL. ASOCIADA A FOLICULITIS AGUDA.

FECHA DE LECTURA: 06-12-2018
ALC

DRA. MONICA YAMBAY
PATOLOGA HPGDR.