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CASE REPORT

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Melkersson–Rosenthal syndrome: A case report

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Key Clinical Message

Melkersson–Rosenthal syndrome (MRS) remains an enigmatic pathology due to an unknown etiology. Our report, of a 69-year-old man with MRS misdiagnosed for about 40 years, underlines the diagnostic difficulty of this condition. A holistic view of the patient, with a correct medical history investigation, are often decisive in the diagnosis of MRS.

Abstract

Melkersson–Rosenthal syndrome (MRS) is a rare disorder with a still unknown etiology. It is defined by three main symptoms, which are orofacial granulomatosis (OFG), facial palsy, and fissured tongue. It generally presents in young people, during the second or third decade, and its incidence in the entire population is about 1%. We focus our attention on a 69-year-old man who came to us with an important swelling of the upper lip. His anamnesis revealed that he suffered from a facial palsy four times in his life and at the physical examination we attested the presence of scrotal tongue. We suspected a misdiagnosed MRS and we searched the web in order to give him a diagnosis and a therapy. We found that OFG is the most common symptom of MRS and that it can show as a non complete form, where the three main symptoms cannot occur simultaneously. We also prescribed a therapy based on the use of topic steroids and antiviral, according to literature. After the positive response to the therapy and according to data found in the most recent literature, we can assume that our patient suffers from a misdiagnosed MRS for about 40 years.

KEYWORDS

intralesional steroids, lip edema, Melkersson–Rosenthal syndrome, Miescher cheilitis, orofacial granulomatosis, relapsing facial palsy, therapy

1 | INTRODUCTION

Melkersson–Rosenthal syndrome (MRS) is a rare neuro-mucocutaneous disorder associated with three main symptoms, which are recurrent orofacial swelling, relapsing facial palsy, and fissured tongue. Its etiology is still unknown; it is suggested that viral infections, allergic factors, and hereditary genes[1] can be associated with the spread of the disease. Many authors suggest that it could be an autoimmune disorder, due to the high positivity

to the anti-SS-A, anti-RNP autoantibody,[2] and elevated serum levels of the angiotensin converting enzyme.[3] Orofacial swelling, also defined as orofacial granulomatosis (OFG), is a condition that can interest the entire face of the patient, and it is characterized by edema of the soft tissues, histologically defined by the "presence of non-caseating epithelioid cell granulomas undistinguishable to sarcoidosis and Crohn disease."[4] If the swelling pertains to the lips—in the most of the cases only the upper—we can refer to OFG as granulomatous cheilitis (GC), and it represents the most common symptom of MRS. Facial palsy is often clinically confused with Bell's palsy, even if this kind of paralysis can be bilateral and more severe than Bell's one.[5] Another symptom that occurs infrequently is facial palsy. Fissured tongue or "lingua plicata" is an idiopathic condition that can be congenital and benign, but, if associated with at least one of these two symptoms—and in particular with GC—can be characteristic of MRS. Concerning epidemiology, MRS has no racial and/or geographical preference, whereas prefers women,[4] like autoimmune diseases, supporting this origin as its pathogenesis. Here we present a case of a 69-year-old man with MRS misdiagnosed for about 40 years, with focus on the diagnostic workup, this syndrome being rare and easily misdiagnosed.

1.1 | Case Presentation

A 69-year-old male patient went to our observation for a condition of recurrent swelling on the upper lip. Anamnesis was positive for Type 2 diabetes. He reported four episodes of facial paresis in his life, about one each 10 years. On objective examination it was possible to see the presence of fissured tongue (Figures 1 and 2) and an erythematous and swelling upper lip present from about 3–4 years (Figure 4). The patient reported us that from some years, every 4–6 months he had very similar episodes at the lip level and that they were treated with systemic betamethasone (2 mg for 3 days and 1 mg for 2 days) by his family doctor, without a precise diagnosis being made.

We suspected a case of MRS, given the association with the three condition, and we suggested the patients follow-up visits. We prescribed topical and systemic corticosteroids in case of other episodes of facial paresis and/or swelling of the lip. At the time of the visit, the patient was suffering from herpetic infection in the upper lip, as can also be seen in Figures 1 and 3, therefore acyclovir 200 mg for five times a day for 7 days was prescribed. An analysis of the literature has been made in order to establish if our patient suffers from MRS.

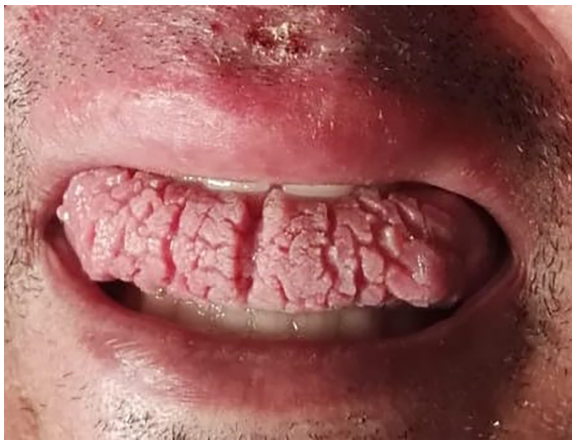

FIGURE 1 Scrotal or fissured tongue or lingua "plicata": considered as a developmental malformation, it can be idiopathic or, in presence of the other two symptoms, a characteristic of MRS.

2 | DISCUSSION

2.1 | Main symptoms and their presentation

MRS is a rare disorder characterized by a triad of symptoms, which classically are orofacial granulomatosis, facial palsy, and lingua plicata. Historically, the first case of this disease was observed by Melkersson in 1928 in a woman presenting lip edema and intermittent peripheral facial palsy; subsequently, Rosenthal in 1931 noted the presence of fissured tongue in these kind of patients, and added it to the list of the symptoms, defining the MRS.[4,6,7] When all these symptoms occur simultaneously, it is very easy to make diagnosis. Unfortunately, MRS can show as a mono- or oligosymptomatic disorder, in fact, in most cases, the MRS syndrome often does not present the classic clinical triad, which is why it is difficult to diagnose.[7–9] In the literature, several cases of manifestation of MRS with gingival onset are reported, in the absence of local and systemic signs and symptoms.[10,11] In fact, the oral cavity can often be a sign of pathologies.[12] The most frequent symptom is orofacial granulomatosis (OFG), which is reported in 80%–100% of MRS diagnosis.[6] OFG is defined as an uncommon and chronic inflammatory condition of unknown etiology[7] that affects intra and extraoral mucosal tissues of the head and neck. The site it hits the most is the upper lip, then it can affect the lower lip, the cheek, the buccal mucosa, the eyelid and can even have a wider involvement of the whole face of the patient.[6,9] In the event of only interest of the lips, it can be referred as cheilitis granulomatosa (CG). It is well supported from literature that the edema characterizing OFG and CG is typically

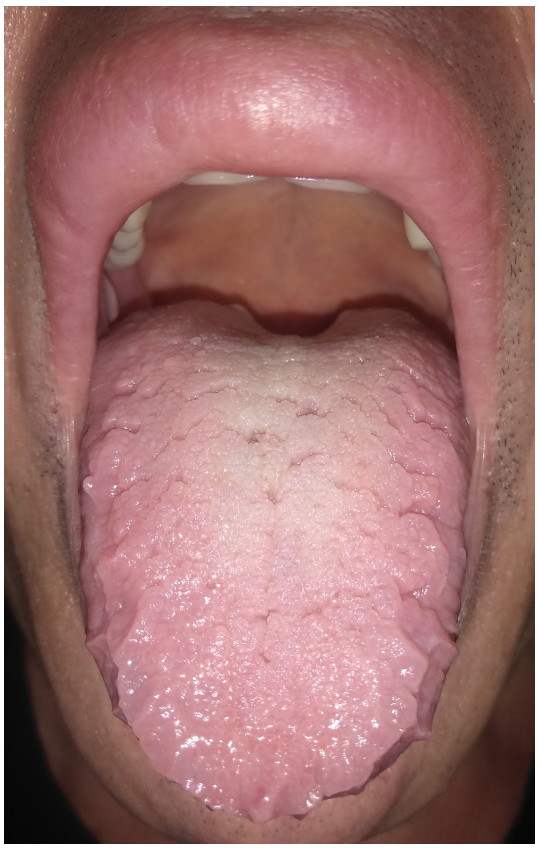

FIGURE 2 Focus on patient's tongue and upper lip: note the scrotal tongue and the increase in volume of the upper lip.

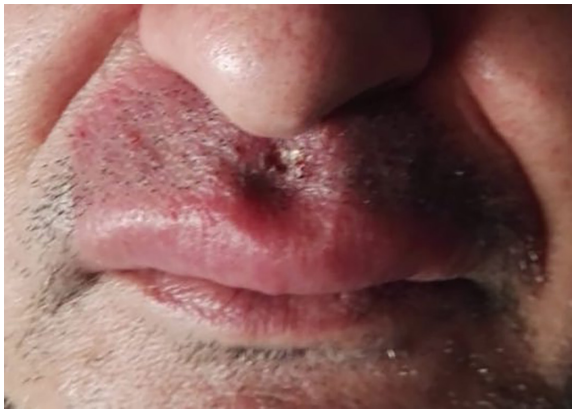

FIGURE 3 Extraoral view of the upper lip of the patient: note the lip edema and the erythema. It can be also noted the ulceration maybe due to HSV-1 concomitant infection.

acute, painless and non-pitting and histopathologically marked out by the presence of noncaseating epithelioid cell granulomas and lymphedema.[4,5,7,8,10–14] There is disagreement in literature about the definition of OFG and CG: CG is a chronic swelling of the lips—one or both simultaneously—due to granulomatous inflammation which was described by Miescher for the first time in

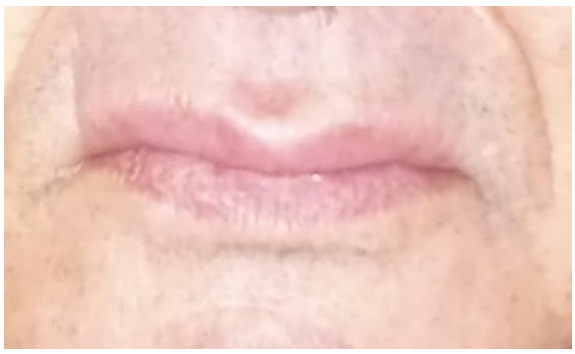

FIGURE 4 Extraoral front view of the patient's upper lip: note the complete regression of the swelling and of the erythema.

1945—and so called Miescher's cheilitis, too.[4,7] OFG is a term used for the first time in 1985 by Wiesenfield that encompasses both MRS and CG.[4,7] Histopathologically, these two conditions are very similar, and they can present or not noncaseating epithelioid cell granulomas indistinguishable from Crohn's disease or sarcoidosis.[4] That is the reason why histology cannot be considered the gold standard for a diagnosis of CG or OFG. Indeed, it is well understood that both OFG and CG could represent a monosymptomatic form of MRS,[4] where CG definitely is the most frequent form of presentation. Patients with OFG or CG should be in any way investigated for Crohn's disease, too, as the association with this disorder is well established in literature,[15] and in order to rule out one disease or other. Thus, some authors believe that CG or, more in general OFG, is very rare if in association with Crohn's disease—about 0.05%—[7] and they assert that CG can be seen as a subtype of MRS. MRS can show as a oligosymptomatic form too, and in this case, facial palsy is the second more common symptom. According to data found in literature, facial nerve paralysis occurs in 30–80% of patients.[6,9] Clinically, it can be confused with Bell's palsy, and this takes to a misdiagnosis of MRS. Facial nerve palsy presents more often as a unilateral and relapsing, partial or complete paralysis of the seventh nerve. Episodes of paralysis usually last longer than Bell's ones, and have worse prognosis, as this kind of palsy can lead to fibrosis of the neural tissue.[9] Moreover, in some cases the lesion can affect other cranial nerves, defining other kind of neuropathies such as tinnitus or hearing loss (with the involvement of the VIII cranial nerve), migraine (with the involvement of V cranial nerve), and dysgeusia (with the involvement of IX cranial nerve).[5,9] The last symptom associated with MRS is lingua plicata, or scrotal or fissured tongue. It is considered as a developmental malformation with an estimated incidence of 0.5%–5% in the general population.[9,14–16] It can also be idiopathic and not involved in MRS, but, according to data from literature,

30%–80% of patients with suspected MRS shows a fissured tongue.[9,15,16] In the presence of two of these three symptoms, it is quite clear that the patient suffers from MRS. MRS can be defined as a clinical syndrome[9,16–19] which means that it does not require histology for establishing a diagnosis. As already said before, there are no typical histological features that can assure a diagnosis of MRS, and at the same time, there are no specific biomarkers or imaging tests that can confirm a certain diagnosis. A recent study by Gaviano et al. examined the histopathological aspects of the oral lesions of 47 patients affected by MRS to better define the histopathological characteristics following the non-negligible difficulty of diagnosing MRS. The results showed that the most common biopsy site was the upper lip, followed by the lower lip, gingiva, and palate. The most important findings were ill-defined and well-formed granulomas. Lymphoplasmacytic inflammatory infiltrate has been observed in the early and late stages of MRS. Edema, fibrosis, vasodilatation, and congestion were the most common findings in the lamina propria. Gingival and palatal examinations also revealed granulomatous infiltrates. Thus, histopathologic examination of oral manifestations is helpful in diagnosing MRS; the absence of granulomatous inflammation does not rule out the diagnosis of the syndrome. Clinical and histopathologic analysis of rare gingival and palate lesions are important, as all histopathologic findings of disease have been found at these sites.[18,19] It can be assumed that MRS is a clinical and of exclusion diagnosis.[9]

2.2 | Epidemiology and etiology

MRS is a rare disease that affects 0.08% of the worldwide population,[4,5,8] but it is still considered as a mis- and underdiagnosed disease because of its unclear presentation. As mentioned before, when in presence of one symptoms only—or sometimes two—it can be very difficult to make diagnosis. That is the reason why there is agreement in literature that the incidence could be higher.[9] It is also reported that it is even rarer in childhood.[9] As the disease could present as a mono or oligosymptomatic form, a delay of 4 years in average in the diagnosis of MRS can be found.[5] Its etiology is still uncertain, and genetics, immunological disorders, infective origins, and food or atopic reactions are taken in count. About this last topic, there is a little evidence that in some cases MRS—especially the OFG symptom—can be associated with intolerance to cinnamon and benzoates.[4,7] These data can be regarded, but they still need further investigations. Another hypothesis that longs to be more analyzed is that MRS can be seen as an early manifestation of mixed connective tissue diseases (MCTD), such as systemic lupus erythematosus or sclerodermia.[2] According to this theory, MRS can be seen as the primary manifestation of a wider disease, with a bigger involvement of the neurological functions and of the whole body.[4] This theory is also in need of a major in-depth analysis.

It seems quite clear instead that MRS undergoes to a male-to-male vertical transmission.[19] Genetics play a fundamental role in the expression of the disease, as it is demonstrated by Xu et al.[19] in their study of a Han Chinese family, where the authors found that a mutation in a gene of a fatty acid transport protein (FATP-1), a protein responsible for the fatty acids uptake and metabolism and robustly expressed in skin, happened. This suggestion is also confirmed by another study conducted in a Tunisian family by Mansour et al.,[16] where a paternal and a genetic inheritance as an autosomal dominant disease is proposed, according to Lygidakis et al.[18] and Xu et al.[19] However, there is no complete agreement in this genetic theory: Pei et al.[13] suggest that genetic heterogeneity or genetic modifiers such as female hormones (in agreement with Elias et al.,[5] too) can be considered as the causal factors in the etiology of MRS, as their cluster of patients with certain diagnosis of MRS did not present the FATP-1 mutation.[10] This means that there is still the need of more studies of the genetic causes.

Talking about incidence, according to Wehl et al.[4] and Zewde,[6] it more often presents during the second or third decade, and it prefers women rather than men. As young women are preferred, this leans toward an autoimmune etiology, where sex hormones together with predisposing factors[9] can cause the disease. An infective origin of the disorder is also under debate: many authors[6,8,9,12] believe that a viral or a bacterial infection can behave as a trigger to the manifestation of the disease, which sparkles the immune system giving rise to an abnormal response against nonself antigens.[9] In the analyzed literature, patients were screened in order to rule out other concomitant infections, such as *EBV, ZVZ, CMV, HSV, or M. tuberculosis, B. burgdorferi*. In the light of these events, there is an interesting and brand new association with the infection of the SARS-Cov-2 virus and MRS. COVID-19 pandemic is nowadays the most important sanitary issue every Nation is fighting. Beyond the typical pulmonary presentation of the disease, it is well established that it can affect the entire body and so the mouth, too. It is strongly supported that the virus enters the human cells through the angiotensin converting enzyme 2 (ACE-2) receptors, which are extremely represented in the lungs, in the salivary glands and in the surface of the tongue.[17,18] After the colonization, in predisposed patients it leads to the cytokine storms and the

pulmonary disease characterized by a glass appearance of the chest in x-rays and TC scan.[20] As it affects primary the tongue, it is quite clear that it can cause oral lesions, too. Hence, the typical lesions caused by COVID-19 infection in the oropharyngeal tract are dysgeusia and ageusia, ulcerations and petechiae of the whole oral cavity and geographical tongue.[21] The association between MRS and COVID-19 infection is reported in few cases in literature until now. Taslidere et al.[8] reported a case of a 51-year-old woman with diagnosed MRS who came to their attention with swollen lip and SARS-Cov-2 symptoms. A series of laboratory test revealed that she suffered from COVID-19 infection and that the swollen lip, histopathologically defined as presenting areas of inflammation involving granulomas, Langhans giant cells and mast cells, could be referred as an exacerbation of MRS. Mast cells are believed to be the link between the manifestation of COVID-19 symptoms and MRS, because of their role in the occurrence of the immune response. Mast cells activate the inflammatory response giving rise to the cytokine storm which verifies during the manifestation of the disease.[8] RCP is another protein being part of the cytokines that is believed to play a role in the manifestation of MRS related to COVID-19 infection. High RCP levels are detected in COVID-19 patients and in MRS patients, too.[20,21] Nevertheless, this hypothesis of association with infections—and in particular with SARS-Cov-2—needs further investigations.

2.3 | Therapy

According to literature, a standardized therapy for symptomatic MRS does not exist. Most authors suggest corticosteroids in order to decrease facial swelling and to reestablish the compliance of the seventh nerve. Use of topic or systemic corticosteroids depends on the severity of the disease.[22] A long-term therapy (about 3–6 weeks) with prednisone or triamcinolone is usually prescribed.[4,9] Interestingly, there is quite agreement in literature that MRS' facial palsy does not respond to antihistamines drugs,[5,9] and that this factor can contribute to rule out Bell's palsy in a differential diagnosis. Thus, Zewde[6] reports that antihistamine drugs can be used as a therapy in MRS, too. This is controversial and needs further investigations. When triggered by infections, as in the case of MRS related to COVID-19, giving a therapy for the primary infection can reduce and eliminate all the symptoms of MRS, as demonstrated by Taslidere et al.[8] A recent literature review described several treatment options including as glucocorticoids, immunosuppressants (azathioprine, methotrexate, thalidomide, tacrolimus), antituberculosis agents (ethambutol, isoniazid), antimalarials (chloroquine), antileprosy drugs (clofazimine and dapsone), metronidazole, antibodies monoclonal anti-TNF-α (infliximab, adalimumab), sulfasalazine, antibiotics, and nonsteroidal anti-inflammatory drugs (NSAIDs).[23]

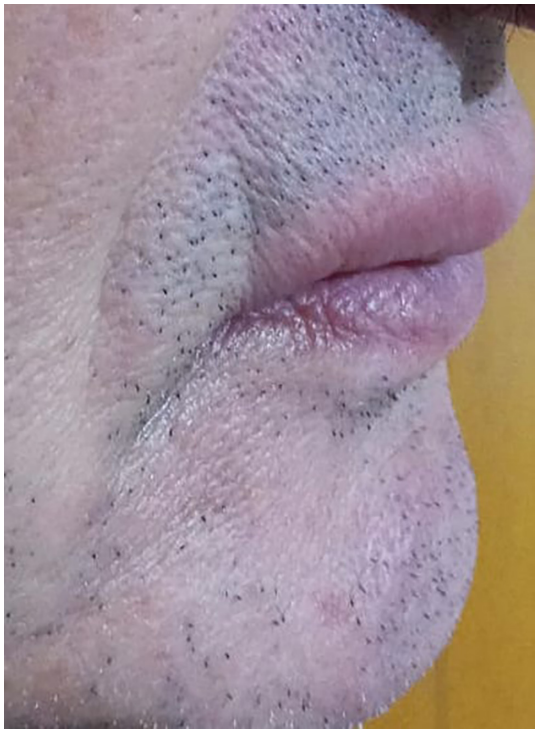

FIGURE 5 Extraoral lateral view of the upper lip: note the complete regression of the swelling.

3 | CONCLUSIONS

We tried to analyze our patient's symptoms as three distinct units, considering he could suffer from Bell's palsy and CG. Lingua plicata, as already said before, can be considered an idiopathic feature. We referred at the most recent literature in order to provide a correct diagnosis for our patient's symptoms. In the light of the events, we can assume that our patient suffers from a MRS which has been misdiagnosed for about 40 years, because of its oligosymptomatic manifestation and its rare incidence in the population. Even the therapy given for the lip swelling is correct, according to literature. Interestingly, our patient responded positively to the topic corticosteroids, and in only 5 days he referred a complete regression of the swelling of the upper lip (Figures 4 and 5). Informed consent was obtained from the patients also for the use of the pictures in the manuscript. Ethical approval were waived for this study because it is a report of a case, in which no experimental therapy was prescribed.

AUTHOR CONTRIBUTIONS

Mara Pinna: Conceptualization; data curation; formal analysis; writing – review and editing. **Germano Orrù:** Resources; software. **Gloria Denotti:** Supervision; validation; visualization. **Martina Salvatorina Murgia:** Formal analysis; investigation; methodology. **Cinzia Casu:** Software; supervision; validation.

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CONFLICT OF INTEREST STATEMENT

Authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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