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Case Report

Melkersson-Rosenthal syndrome with underlying sarcoidosis in a middle aged female patient

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Abstract Melkersson-Rosenthal syndrome (MRS) is a rare entity. It is often described as a triad of facial swelling, facial nerve palsy and a plicated tongue, but may be diagnosed when two of the above symptoms are seen. It is characterized by a granulomatous inflammation on histological examination and hence disorders such as Sarcoidosis, Inflammatory Bowel Disease and Tuberbulosis are implicated in the etiology. Response to treatment can be disappointing, with most patients having recurrent episodes over a chronic course. Here we present a case of a 45 year old woman who presented with gradual orofacial edema for the last 7 months which she first noted after her Covid vaccination. It was followed by the appearance of left sided facial nerve palsy. Upon investigation, we found radiological evidence of pulmonary sarcoidosis and raised serum Angiotensin Converting Enzyme levels. A biopsy from her lip showed granulomatous inflammation. We treated her with high dose systemic steroids, Mycophenolate Mofetil and Methotrexate. The combination of orofacial edema, facial nerve palsy and a fissured tongue (together called the Melkersson–Rosenthal syndrome) remains a rare presentation with less than 40 cases having been reported in literature. Investigating the patient may uncover an underlying diagnosis of a systemic granulomatous disorder such as Sarcoidosis, or other etiologies including infections and autoimmune conditions. There are no established guidelines towards treatment and the choice of therapy depends upon an individual case-by-case approach and the physician's discretion.

Key words
Melkersson-Rosenthal syndrome; Sarcoidosis; Orofacial edema; Facial nerve palsy.

Introduction

Melkersson-Rosenthal Syndrome (MRS) is a rare disease characterized by the clinical triad of orofacial edema, facial nerve palsy and a fissured or plicated tongue. However, all three symptoms are present concurrently in only 25% of the cases, with the presence of any two symptoms being sufficient for a clinical diagnosis. The commonest of these is usually edema of the face, being seen in 80-100% of the cases.[1] Because of the rarity of the condition, the true incidence of MRS cannot be assessed. There is very little literature available on the subject in our region.

The etiology of MRS has not been clearly elucidated, but studies show strong associations with Inflammatory bowel disease, including both Crohn's disease and Ulcerative Colitis,[2] Sarcoidosis,[3] and a genetic predisposition, with some familial cases having been recorded in literature.[4] The histopathological analysis of MRS demonstrates granulomas with a lymphoplasmacytic infiltrate, and in late stages, may comprise only of fibrosis with absence of granulomatous inflammation.[5] The treatment options for MRS are multifold, but show variable response and no guidelines have been developed yet. These include the use of systemic

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and intralesional steroids, a variety of immunosuppressants, and surgical debulking where required. The condition may resolve spontaneously, but patients often have a chronic course with multiple episodes.

Case report

We present the case of a 45-year-old woman who presented to us via the outpatient department, with the complaint of having generalized facial swelling for the last 7 months. The patient had received the first dose of Covid vaccination around 7 months ago. Shortly afterwards, she began to notice a swelling on her lips and eyelids. The swelling was gradual in onset and increased progressively until it had involved the entire face. There was no associated pain or fever. As the swelling grew, she was unable to close her eyes fully and noticed some difficulty in chewing food. She had conjunctival injection and epiphora in both eyes. She was previously on calcium channel inhibitor drugs for hypertension but there was no other significant medical history elicited. There was also no history of trauma, any infections or a general decline in health. There was no history of any TB contacts, and no history of night sweats and weight loss. She also had no respiratory or gastrointestinal symptoms. The patient had been prescribed antihistamines and multiple courses of antibiotics by the time she reached us, but none had resulted in improvement.

We investigated this patient with a differential diagnosis of Angioedema, Granulomatous Chelitis, Sarcoidosis, Cutaneous Tuberculosis and other causes of macrocheilia. Her complete blood count showed a low total leukocyte count (TLC) of $3.1x10^3$ /uL, with normal differential counts. ESR, serum urea and electrolytes were within normal ranges. Liver tranaminases were slightly elevated. An ultrasound of the face and

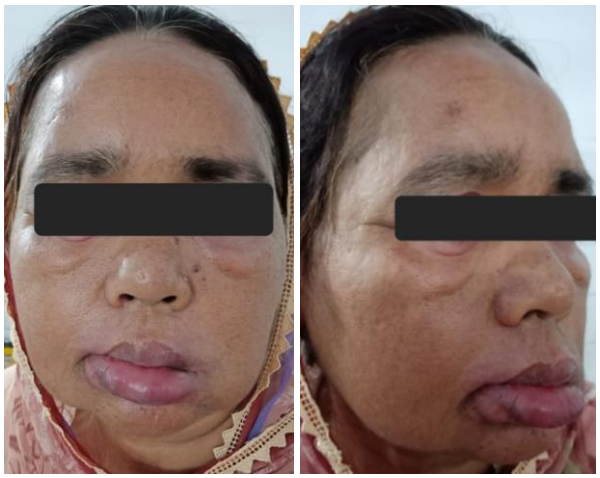

Figure 1 Front and lateral profile views of the patient, showing orofacial edema, macrocheilia and deviation of the angle of mouth.

lip showed only soft tissue edema, with no abnormalities of vasculature and no atypical deposits. We took a biopsy sample from her lower lip and our histopathological examination showed granulomatous inflammation. Distinct epithelioid granulomas in the deep dermis were visualized, without any evidence of caseation necrosis or tubercle bacilli. Another biopsy done from the forehead region was inconclusive. A chest x-ray displayed some vague opacities in bilateral lower lobes. We followed it up with a High Resolution CT (HRCT) scan of the chest, on which we found a few calcified granulomas in the posterior segment of left upper lobe, calcified subcentimeter left hilar lymph nodes, bilateral apical pleural thickening, bilateral subpleural reticulations and a ground glass haze involving lower lobes. Further testing revealed a positive Interferon Gamma Release Assay (IGRA). Her Serum Angiotensin Converting Enzyme (ACE) levels were twice the upper limit of normal, at 106.3 U/L. All other labs, including thyroid function tests and complement levels were normal.

Considering the positive IGRA and the endemicity of Tuberculosis in the region, we did initially suspect Tuberculosis, but a trial of anti-tuberculosis therapy resulted in no improvement.

Later, the findings on histopathology, HRCT chest and serum ACE levels led us to a conclusive diagnosis of Sarcoidosis and we started this patient on 30mg daily of oral Prednisolone.

During this period of investigation, while the patient was on follow up with us, she suddenly developed deviation of the angle of the mouth on the right side, slurring of speech and inability to chew from the left side. Upon examination, we found that she had developed left sided facial nerve palsy of the upper motor neuron type. She also had mild fissuring of the tongue present. Due to the successive occurrence of orofacial swelling and facial nerve palsy, with granulomatous inflammation seen on histology, we diagnosed this patient with Melkersson Rosenthal Syndrome. Following the neurological deficit, we increased her daily steroid dose to 60mg of prednisolone, in collaboration with a neurology consult, and also started her on Mycophenolate Mofetil. 6 weeks of this treatment brought significant decrease in the facial swelling, but no improvement in facial nerve function. As her TLC and liver transaminases have now settled down within normal ranges, we have switched the patient to Methotrexate in the hope of achieving a better response, and she continues to be on regular follow up in our OPD.

Discussion

MRS is a rare disorder with less than 40 cases having been reported in literature. It shows no ethnic or geographical predisposition, but does have slight female preponderance. Most cases appear among young adults. MRS is characterized by a clinical triad orofacial edema (described in some texts as granulomatous cheilitis), facial nerve palsy, and fissured tongue or lingua plicata. MRS is diagnosed by the presence of any two out of these three symptoms, or the combination of orofacial edema and non-caseating granulomas on histopathological examination.[9] MRS can present with monosymptomatic or oligosymotomatic forms, with facial or labial edema being the most common complaint. It is seen in up to 80% of the cases. The edema is typically non-pitting and painless, centered around the perioral area. Facial palsy is found in up to 60% of the cases, and may precede the diagnosis of MRS by several years. Finally, a fissured or scrotal tongue is the least common symptom, seen in only 35% of the cases.[10] Only 25% of the cases have all three symptoms present at the same time. The symptoms can spontaneously resolve in some cases, but usually recurs with multiple episodes.[3]

The cause of MRS has not been clearly elucidated, but studies have shown links to a wide variety of conditions. These include granulomatous disorders such as sarcoidosis and Inflammatory Bowel Disease (IBD), infections such as HSV1, Tuberculosis(TB) and Leprosy, autoimmune conditions such as thyroiditis and many others.[6] There was also a reported case of MRS occurring after a Covid-19 infection.[11] Granulomatous conditions that involve the orofacial area, such as IBD, sarcoidosis, and mucocutaneous Tuberculosis are also included in the differential diagnoses of MRS, as well as angioedema, facial trauma, Bell's palsy, contact dermatitis, granulomatous blepharitis and others.[7] Our patient had no history of gastrointestinal or pulmonary symptoms, pre-existing defect in the central or peripheral nervous system, trauma to the region, unusual cold or heat intolerance, weight loss, or fever. Upon investigation, we found no evidence of active infections. Because of the positive result of Interferon Gamma Release Assay, we did initially suspect Tuberculosis as a primary etiology and gave the patient a trial of anti tuberculous therapy. However, the patient did

not respond to that line of treatment. Raised ACE levels, findings in HRCT chest, and supportive histological findings led us to the diagnosis of underlying Sarcoidosis.

There is also a genetic component in the etiopathogenesis of MRS, with reports of several familial cases. Recently studies have shown a statistically significant rise in the expression of HLA Ax02, HLA DRB1x11, and HLA DQB1x03 in cases of MRS as compared to controls, and this lends further credibility to the possibility of a hereditary predisposition.[3] In our patient, a detailed family history did not elicit any prior cases with similar symptomology in close or extended family.

On histopathological examination, MRS in the early stage, particularly the first five years of disease presentation, usually displays non caseating granulomas, both epithelioid and non epithelioid, ranging from ill-defined to discrete forms. They are accompanied by an inflammatory infiltrate which comprises of lymphocytes, and on occasion, plasma cells. The infiltrate is enhanced in a perivascular distribution. Granulomatous inflammation is seen in 46-82% of the cases and its absence does not exclude the diagnosis. In the later stages of disease, fibrosis is often seen with a few scattered and indistinct granulomatous structures.[3] For our patient, we took a biopsy sample from the swollen lower lip. Our specimen from the labial mucosa showed granulomatous cheilitis, with non-caseating epithelioid granulomas visualized in the reticular dermis. There were also accompanied with a predominantly lymphocytic infiltrate. An enlarged nerve surrounded by lymphocytic infiltrate was also seen.

The treatment of MRS is largely based on the use of systemic steroids and immunosuppressants. While there are no guidelines in place yet, the use of oral corticosteroids brings about improvement in up to 80% of the patients and reduces the relapse rate by 60-75%. A short course of oral prednisolone or pulse therapy with intravenous methylprednisolone is usually prescribed. In cases where no systemic granulomatous pathology has been detected, the use of intralesional triamcinolone is preferred. The use of doxycycline, methotrexate, intravenous immunoglobulins, antimalarials and TNF-a inhibitors has also been described in some cases. Ancillary treatments such as vitamin supplements and specific dietary modifications have also been employed.[6] Other treatment options include minocycline, clofazimine, dapsone, NSAIDS, danazol, thalidomide, and sulphasalazine. surgical options include cheiloplasty, and facial nerve decompression.[8] These patients are usually managed by a multidisciplinary team with a collaborated effort by dermatologists, otolaryngologists, neurologists, ophthalmologists, and surgeons. Despite the multitude of treatment options employed, the course of MRS can be often unpredictable, with recurrences and relapses over a course of many years.

Conclusion

The combination of orofacial edema, facial nerve palsy and a fissured tongue (together called the Melkersson‑Rosenthal syndrome) remains a rare presentation with less than 40 cases having been reported in literature. Investigating the patient may uncover an underlying diagnosis of a systemic granulomatous disorder such as Sarcoidosis, or other etiologies including infections and autoimmune conditions. There are no established guidelines towards treatment and the choice of therapy depends upon an individual case-by-case approach and the physician’s discretion.

Declaration of patient consent The patient has given appropriate consent for the publication of this case report. She and her guardians understand that their names and initials will not be shared. While an effort will be made to conceal her identity, absolute anonymity cannot be guaranteed.

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Conflict of interest Authors declared no conflict of interest.

Authors' contribution

AS,AT,HS: Identification and management of the case, manuscript writing, has given final approval of the version to be published.

WS,IH: Diagnosis and management of the case, critical review of the manuscript, has given final approval of the version of the manuscript to be published.

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