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CASE REPORT

Oligosymptomatic form of Melkersson-Rosenthal Syndrome possibly triggered by COVID-19 infection: A case report

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Introduction: Melkersson Rosenthal syndrome (MRS) is a disease of multifactorial origin typically presented with a triad of symptoms including peripheral facial nerve paralysis, plicated tongue and orofacial edema. Diagnosing MRS requires the exclusion of other granulomatous diseases and the correlation of clinical with histopathological finding.

Case presentation: We present the case of a 56-year-old female with a four-month history of lower lip and right mandible angle swelling together with a plicated tongue that appeared during COVID-19 infection. The patient was successfully treated with intralesional Triamcinolone Acetonide at a dose of 40 mg.

Conclusion: The presented case is specific by its late onset since the patient experienced their first symptoms in fifties, which differs from the majority of cases where the diagnosis is usually established in young adults. Infectious factors are established as possible etiologic factors of MRS, but few cases are described to be triggered or worsened by COVID-19 infection.

Keywords: Melkersson-Rosenthal syndrome, granulomatous cheilitis, COVID-19, oligosymptomatic

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Introduction

Melkersson-Rosenthal syndrome (MRS) is a rare inflammatory, immune-mediated neurologic disease typically manifested by the plicated tongue, peripheral facial nerve paralysis and orofacial swelling [1].

To diagnose MRS in a patient with persistent orofacial edema requires the presence of at least one of the other two mentioned symptoms, together with the exclusion of main differential diagnoses - Crohn's disease and sarcoidosis. Only one of the two clinical features is sufficient for diagnosis in the presence of histopathological evidence of granulomatous cheilitis in the biopsy of the eyelid or the lip [2].

The onset of the disease is most common in young adults, especially in the second and third decades of life, slightly more common in women than in men [2, 3]. The etiology of MRS is not fully understood, but it is postulated to be influenced by various factors, including genetics, infections and allergic factors [4-6].

We report a case of a patient with an oligosymptomatic form of MRS that occurred during SARS-CoV-2 infection. Remission was achieved after intralesional treatment with Triamcinolone acetonide (TA).

Case presentation

A 56-year-old female presented with a four-month history of diffuse, tense, non-pruritic lower lip and right mandible angle swelling (Figure 1A), with no history of prior swelling episodes, nor peripheral nerve paralysis. The patient reported painful groves on the dorsal tongue surface, which appeared almost simultaneously with lip swelling and didn't improve over time (Figure 1B). Physical examination showed no enlargement of peripheral lymph nodes nor features of peripheral facial nerve paralysis.

From the anamnesis, swelling started shortly after the PCR test confirmed SARS-CoV-2 infection, while the patient was in isolation. She suffered from a mild form of COVID infection, including loss of smell, mild fever and slight difficulties in breathing, and was treated symptomatically with antipyretics and vitamins. The lower lip edema persisted in a milder form during the next four months. When it worsened again, the patient presented to our department. During the period of exacerbation of clinical symptoms, the patient had no other episode of SARS-CoV-2 infection nor verified viral infection of other etiology. Other comorbidities included hypothyroidism, which was treated adequately for years. The physician indicated an allergic testing investigation, which showed non-elevated levels of total serum Immunoglobulins E (IgE), as well as negative results of allergen-specific IgE in the patient's serum. The patient was then examined by the otorhinolaryngologist, which indicated a lip biopsy.

Histopathologic examination of lip biopsy revealed edema of subepithelial connective tissue and scarce perivascular lympho-plasmocytic infiltrate, together

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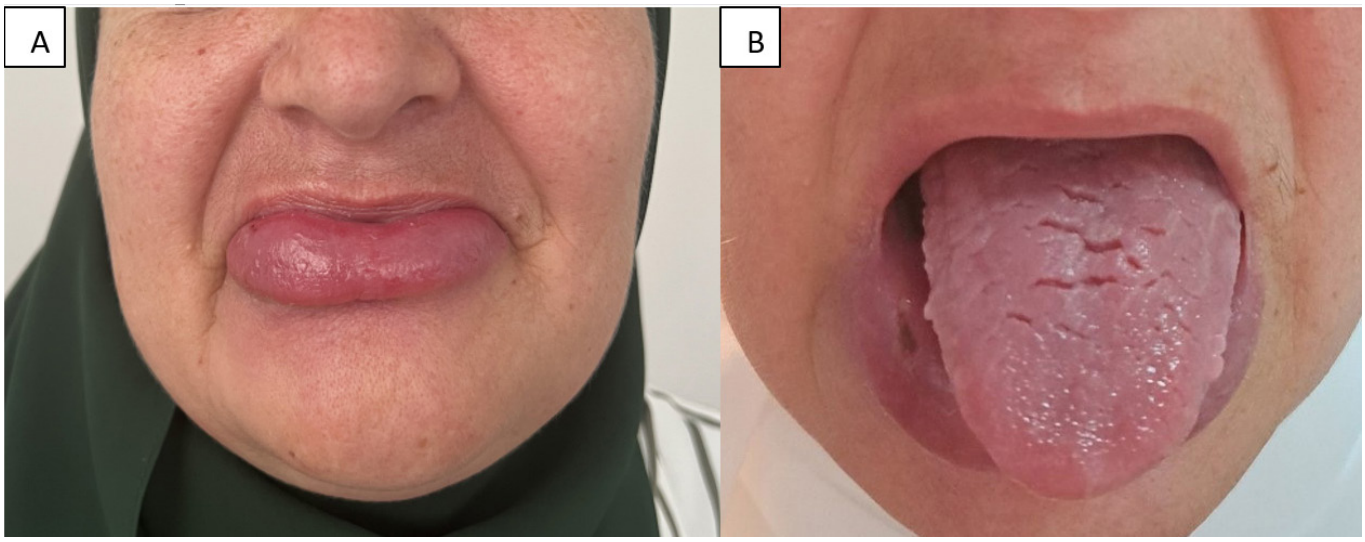

Fig. 1. A. Diffuse and tense swelling of the lower lip; B. Plicated tongue.

with multiple non-caseating epithelioid-cell granulomas consisting of epithelioid histiocytes, multinucleated Langhans giant cells, lymphocytes, plasma cells and macrophages (Figure 2).

To exclude other granulomatous diseases such as sarcoidosis, a chest ray was performed, together with the examination of serum angiotensin-converting enzyme (ACE) levels, which were normal. Because the patient reported occasional digestive interferences (bloating, mushy stools alternating with constipation), gastroscopy and colonoscopy were performed to exclude granulomatous diseases of the intestines.

Based on the above- mentioned findings, the oligosymptomatic form of MRS was diagnosed.

At the first examination, the patient was administered topical corticosteroid therapy with no improvement. The second treatment line was the application of intralesional Triamcinolone Acetonide at a dose of 40 mg. Triamcinolone Acetonide was injected evenly into the lower lip and right mandible angle. Three such weekly injections were given. Three weeks later, the clinical improvement was obvious with a reduction of the edema and softening of the previously described hard consistency of the lower lip (Figure 3). The patient was satisfied and reported significant improvement in the quality of life.

Discussion

Although the characteristic triad of symptoms is a classic clinical presentation, oligosymptomatic and monosymptomatic variants are more common forms of the disease and represent up to half of the cases [7-9]. Monosymptomatic or oligosymptomatic forms of the disease which present with one or two symptoms, are more common in the initial course of the disease since the classic triad of symptoms rarely appears simultaneously [1, 9]. In the presented case, the patient experienced first symptoms in her fifties, which differs from the usual age of disease onset, since the diagnosis of MRS is usually established in young adults, or most commonly between the age of 25 and 40 [1, 3].

The differential diagnosis of MRS includes a broad spectrum of diseases, including many granulomatous and infectious conditions. The most common differential diagnoses are Crohn's disease and sarcoidosis as granulomatous conditions, followed by other neurologic, allergic and dermatologic conditions [7, 10]. To establish the diagnosis of MRS, there is a need for a detailed clinical examination, including a neurologic examination of large cranial nerves, and a search for visual or hearing impairment. To exclude mimics with oral manifestations it is important to consult a gastroenterologist and do a

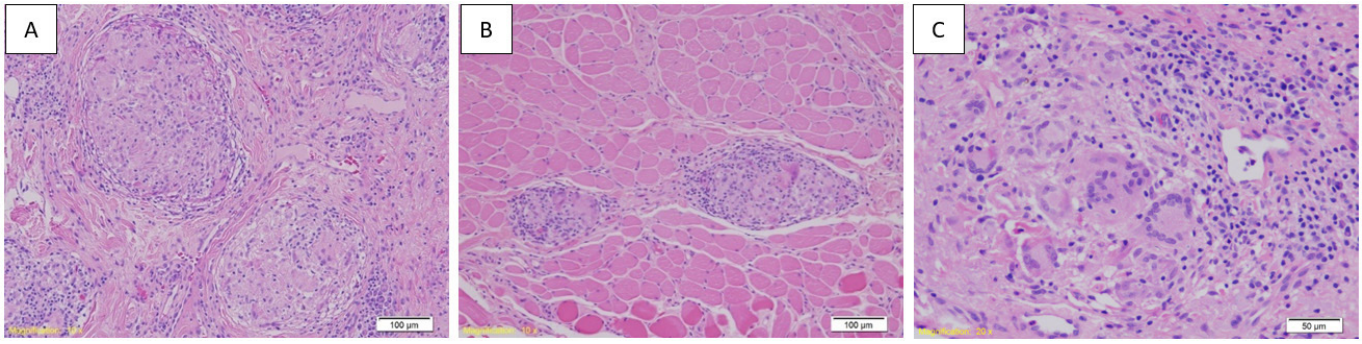

Fig. 2. Multiple non-caseating granulomas in the subepithelial connective tissue (A; H&E, x100) and between muscle fibers (B; H&E, x100) consisted of epithelioid histiocytes, multinucleated Langhans giant cells, lymphocytes, plasma cells and macrophages (C; H&E, x200).

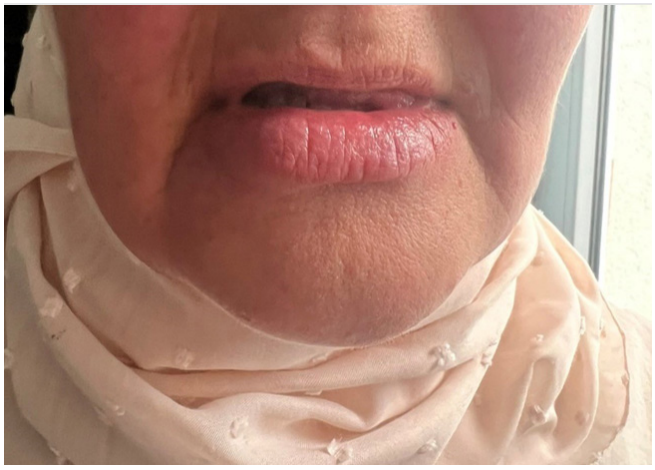

Fig. 3. Significant reduction of lower-lip edema after intralesional triamcinolone acetonide application.

colonoscopy to exclude inflammatory bowel disease [2].

The etiology of the disease is not fully elucidated but is supposed to have a multifactorial origin. The postulated etiological factors can be divided into genetic, immunologic factors- irregular immunological T-lymphocyte response, allergic and microbial factors, hypersensitivity to ultraviolet B radiation [9].

Regarding the microbial causes, MRS can be promoted by many viral but also by fungal and bacterial infections- The most common possible triggers include viral infections such as Epstein-Barr, varicella zoster, cytomegalovirus, herpes simplex [11,12]. According to currently available literature, few cases describe the possible influence of COVID-19 infection on the worsening of MRS [11] or COVID-19 infection as a possible trigger of granulomatous cheilitis [12].

Our patient reported getting infected by SARS-CoV-2 infection just before the onset of the first symptoms of MRS. Some of the previous studies imply mast cells as a possible factor that correlates with COVID-19 and MRS since mast cells induce an inflammatory response and are found to be activated especially by viruses, including COVID-19 infection. Also, mast cells are usually found admixed with lymphocytes and plasma cells in samples of mucosa of patients with cheilitis as a component of MRS [11].

Current treatment options for MRS are symptomatic - based to relief patient's complaints and improve their quality of life. Since the etiology of the disease can be multifactorial, there are no uniform guidelines for treatment.

Corticosteroids are the basis of the treatment of MRS and may be used locally, topically, intralesional or in oral form [2].

Based on our experience, and according to the literature, intralesional triamcinolone acetonide (TA) may be used to reduce local lip edema, especially in cases of orofacial edema as the only clinical presentation or when edema is refractory to oral corticosteroids [13, 14]. We used higher doses (40 mg/ml) of intralesional TA which led to significant improvement with a decrease in the severity of edema, similar to the results of Fedele and colleagues [14]. Other studies suggest lower doses of intralesional TA in combination with lignocaine to reduce pain before intralesional injections [13], while others suggest intralesional betamethasone in combination with antibiotics, especially with inhibitors of synthesis of protein C, as doxycycline and minocycline [15, 16]. Other treatment options for MRS have also been tried, including anti-inflammatory, immunomodulatory, or immunosuppressive drugs, as well as inhibitors of tumor necrosis factor-alpha (TNF-alpha), such as infliximab and adalimumab, especially in patients with underlying Crohn's disease. Refractory cases may require surgery [2, 12].

Conclusion

One of the possible triggers of MRS is infection, especially viruses. According to available literature, it is currently known that SARS-CoV-2 infection can trigger and worsen many conditions, including skin disorders. Further research in this field is necessary, especially to elucidate the pathogenesis of MRS, including the possible impact of COVID-19 infection on the development and progression of this multifactorial disease.

Authors' contribution

NĐ: conceptualization, data curation, writing- original draft, methodology; NČ: conceptualization, methodology, writing- original draft; DŽD: data curation, investigation, formal analysis; AR: data curation, investigation, formal analysis; SH: software supervision, visualization, validation; AP: conceptualization, writing- review & editing, supervision.

Conflict of interest

None to declare.

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