Melkersson-Rosenthal Syndrome Successfully Treated With Adalimumab

Ellen H. de Moll, MD; Mark G. Lebwohl, MD

PRACTICE **POINTS**

- The classical triad of Melkersson-Rosenthal syndrome (MRS), which includes facial nerve palsy, facial edema, and lingua plicata, can present gradually over time and should therefore be kept in the differential of cheilitis.
- Tumor necrosis factor α therapy may play a crucial role in rare granulomatous diseases, including MRS.

Melkersson-Rosenthal syndrome (MRS) is a rare syndrome of facial nerve palsy, facial edema, and lingua plicata that can be difficult to treat. We observed a patient with MRS of 4 years' duration that was unsuccessfully treated with multiple therapies. After a variety of diagnoses were considered at outside institutions, including Bell palsy, we diagnosed the patient with MRS based on clinical presentation of the classic triad. Treatment with adalimumab, a tumor necrosis factor α (TNF-α) antibody, showed improvement and relapse-free progress. Further research is needed regarding the role of TNF-α inhibitors in managing this rare condition.

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Melkersson-Rosenthal syndrome (MRS) is a rare condition comprised of unilateral peripheral facial nerve palsy, episodic or progressive facial edema, and lingua plicata (also known as fissured tongue). Melkersson-Rosenthal syndrome is a subtype of orofacial granulomatosis and often is mistaken for angioedema or pseudoangioedema due to the swelling of the lips and eyelids. We present a case of MRS that cleared in response to adalimumab therapy.

Case Report

A 69-year-old woman presented to our dermatology clinic with facial edema and a fissured tongue of 4 years' duration. These symptoms had failed to improve with doxycycline, tacrolimus ointment 0.1%, and cortisone injections of the upper lip, as well as a balsam-free diet, fragrance-free skin products, and flavor-free toothpaste prescribed by multiple physicians over 4 years. Two weeks prior to the current presentation the patient developed left facial nerve palsy that was diagnosed by an outside physician as Bell palsy, and the patient completed a 7-day course of prednisone 1 day prior to presentation. The patient's medical history was remarkable for type 2 diabetes mellitus controlled with metformin, hyperlipidemia controlled with ezetimibe-simvastatin, and psoriasis. She reported no family history of autoimmune or dermatologic disorders and denied any fever, unintentional weight loss, nausea, vomiting, or diarrhea.

On physical examination, the patient had considerable perioral edema and erythema without warmth or tenderness (Figure 1A). The tongue was fissured with notable scalloping at the lateral margins (Figure 1B). There were no aphthous ulcers or lymphadenopathy, and the remainder of the neurologic examination was normal. The patient had erythematous plaques with scaling on the bilateral elbows. Cardiopulmonary, musculoskeletal, and abdominal examinations were otherwise normal.

Laboratory data revealed an elevated white blood cell count of 17,500/μL (reference range, 4500–11,000/μL), an elevated absolute neutrophil count of 14,018/μL (reference range, 0–700/μL), and an absolute eosinophil count of 0/μL (reference range, 0–450/μL), with the rest of the complete blood cell count within reference range. A basic metabolic panel showed an elevated glucose level of 326 mg/dL (reference range, 70–110 mg/dL), consistent with diabetes and most likely exacerbated by the recent steroid course. A lipid panel was consistent with diagnosed hyperlipidemia (total cholesterol, 236 mg/dL [reference range, <200 mg/dL]; low-density lipoprotein,

From the Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, New York.
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Correspondence: Mark G. Lebwohl, MD, Icahn School of Medicine at Mount Sinai, 1425 Madison Ave, New York, NY 10029 (mark.lebwohl@mountsinai.org).

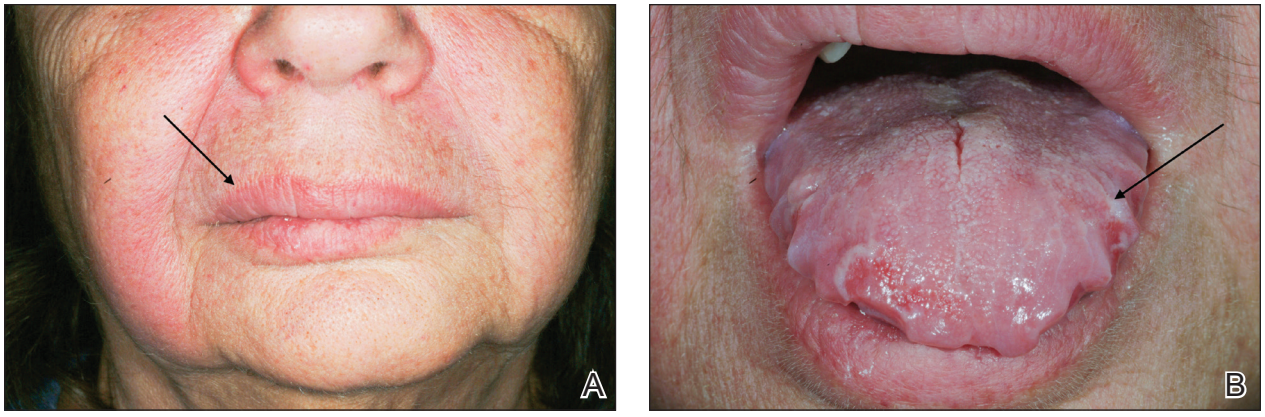

FIGURE 1. Melkersson-Rosenthal syndrome with perioral edema (arrow)(A) and erythema as well as left facial nerve palsy. Lingua plicata also was noted (arrow)(B).

134 mg/dL [reference range, 10–30 mg/dL]; triglycerides, 188 mg/dL [reference range, <160 mg/dL]). Hepatitis B and C tests were negative. A punch biopsy of the buccal and labial mucosa was taken, revealing a parakeratinized stratified squamous epithelium with an unusual pattern of surface keratinization with foci of intracellular and extracellular edema in the spinous layer. The underlying fibrous connective tissue was edematous with infiltrates of lymphocytes, mast cells, macrophages, and a few plasma cells. The pathology report listed the diagnosis as nonspecific "chronic mucositis," with a list of differential diagnoses that included angioedema, hypersensitivity reaction, or other possible autoimmune disorders.

On consideration of these differential diagnoses, it was felt most likely to be MRS, which remains a primarily clinical diagnosis characterized by the triad of symptoms seen in this patient. Treatment of this condition emphasizes inflammation, and steroid therapy often is utilized, as it was in our patient. After the diagnosis of MRS was made, the patient received adalimumab 80 mg subcutaneously on day 1 and 40 mg on day 8 as a loading dose; she subsequently began a course of subcutaneous injections of adalimumab 40 mg once every other week for treatment of psoriasis with the goal of simultaneously treating the MRS. The symptoms did not completely resolve at this dose, so it was increased to 40 mg once weekly. The patient reported that the facial edema, lingua plicata, and facial nerve palsy resolved concomitantly over approximately 3 months with greater improvement at 5 months (Figure 2). The patient has had no relapses as of the last follow-up at 11 months.

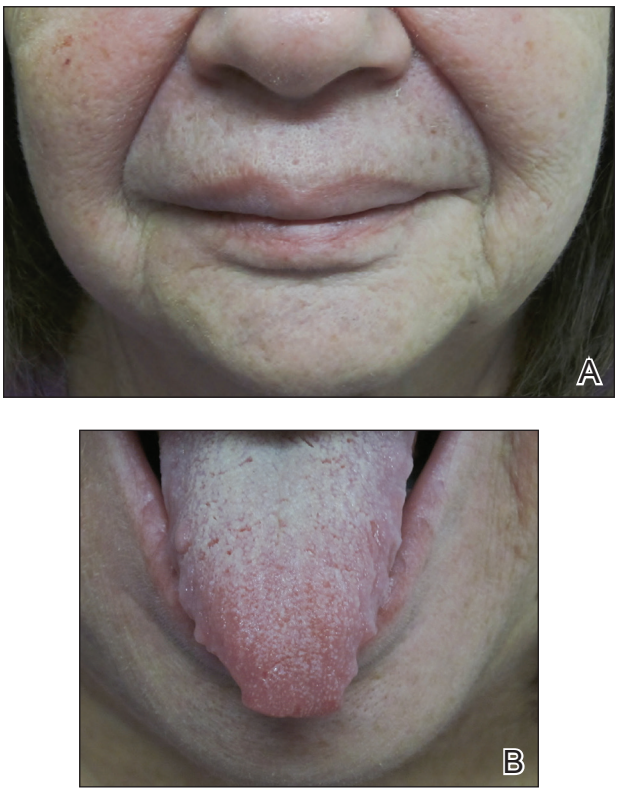

FIGURE 2. At 5-month follow-up after treatment with adalimumab 40 mg once weekly, the patient demonstrated complete resolution of the facial nerve palsy and facial edema (A). The lingua plicata was greatly improved, though some partial scalloping of the tongue border remained (B).

Comment

Melkersson-Rosenthal syndrome usually presents sporadically, though there are reports of familial association,[1-3] and only 8% to 25% of patients worldwide present with the complete triad of symptoms.[4] The pathogenesis of the syndrome is controversial. Granulomatous changes have been found in patients experiencing chronic edema. However, according to Zimmer et al[5] in a study of 42 MRS patients, only 46% (19/42) had granulomatous changes; 36% (15/42) had nonspecific inflammation, 11% (5/42) had incidental findings, and 7% (3/42) showed no histopathologic abnormalities. Granulomatous cheilitis is a subtype of orofacial granulomatosis, an idiopathic process that causes swelling of the face and lips as well as intraoral swelling and ulceration. Orofacial granulomatosis is referred to as granulomatous cheilitis when the lip

is involved. Melkersson-Rosenthal syndrome is another subtype of orofacial granulomatosis that includes facial palsy and fissured tongue.[6,7]

In a clinical study of 7 patients with MRS, Liu and Yu[1] found 3 (42%) patients to have dysarthria, dysphagia, and tongue muscle atrophy; 1 patient to have migraine-like headaches; 1 patient to have decreased vision and an ocular movement disorder; 1 patient to have ipsilateral hearing loss; and 1 patient to lack any other symptoms. Halevy et al[8] suggested a possible association of MRS with psoriasis. In their review of 12 patients, 1 (8%) had psoriatic arthritis, 2 (17%) had skin biopsy–proven psoriasis, and 3 (25%) had a family history of psoriasis.[8] Because the disease is quite rare, it is difficult to determine other symptoms that may be associated with the disease.

Tumor necrosis factor α (TNF-α) is needed for granuloma formation, and TNF-α antagonists have been used to treat a number of granulomatous conditions including Crohn disease and sarcoidosis.[9-11] Two case reports indicate that infliximab, a mouse/human chimeric monoclonal antibody to TNF-α, has been used successfully to clear MRS.[12,13] One report cited the use of adalimumab for maintenance therapy of MRS,[12] and more recently, adalimumab has been reported for refractory MRS.[14] However, there currently are no known reports regarding the efficacy of adalimumab as a first-line treatment of MRS.

Adalimumab is a fully human monoclonal antibody to TNF-α, which is administered via subcutaneous injections. Infliximab must be administered at an infusion center, making treatment logistically more difficult for patients, and can be associated with the development of infusion reactions, though the exact data on infusion reactions are difficult to estimate due to variations in reporting.[15,16]

In 2014, Stein et al[14] reported a case of refractory MRS in a 29-year-old man associated with acute attacks of hearing loss. The patient's symptoms were controlled with high-dose prednisolone but were unable to be maintained on methotrexate or azathioprine as steroid-sparing agents. The patient was loaded with adalimumab 80 mg subcutaneously once on day 1 and was continued on 40 mg subcutaneously once every 3 weeks, gradually extending to once every 4 weeks when symptoms improved. The patient was slowly weaned off prednisolone 16 months after starting adalimumab. After 20 months, adalimumab therapy was discontinued and the patient remained recurrence free at 4 years' follow-up.[14] In another case, adalimumab was utilized as maintenance therapy after initial improvement with infliximab.[12] Kakimoto et al[12] reported a previously healthy 19-year-old woman with edema of the bilateral eyelids and upper lip. The authors determined the patient had MRS despite the lack of fissured tongue or facial nerve palsy and started infliximab. The condition resolved after the patient's second infusion of infliximab and completely cleared after the third infusion; however, she had logistical difficulties reaching the infusion center and disliked the flulike response she experienced with the treatment. She was started on once weekly subcutaneous injections of adalimumab 40 mg and did not relapse.[12] Another patient with granulomatous cheilitis responded to adalimumab after corticosteroids, intralesional injections of triamcinolone, topical tacrolimus, roxithromycin, and clofazimine failed.[17] The patient received adalimumab 80 mg for the first week and 40 mg for the second week and every 2 weeks thereafter. The patient began improving after the third dose and remained relapse free for at least 6 months of follow-up.[17]

Conclusion

We present a case of a 69-year-old woman who presented with facial nerve palsy, facial edema, and a fissured tongue, which is the classic triad of MRS, and all 3 symptoms improved with adalimumab.

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