Melkersson-Rosenthal Syndrome

New Clinicopathologic Findings in 4 Cases

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Objective: To define the clinicopathologic features of eyelid involvement in Melkersson-Rosenthal syndrome (MRS).

Methods: Four patients with eyelid edema consistent with MRS were evaluated clinically, including diagnostic imaging in 2 patients. Eyelid tissue from these patients was examined by light microscopy and immunohistochemistry. Polymerase chain reaction for herpes simplex virus was performed in 1 case.

Results: The 3 men and 1 woman ranged in age from 33 to 74 years. All patients had insidious, painless, nonpitting eyelid edema. Three patients had unilateral edema; one had bilateral, asymmetric involvement. Ipsilateral lip edema was present in 1 case. Computed tomography demonstrated periorbital heterogeneous thickening that corresponded to the microscopic finding of scattered granulomas. All 4 patients demonstrated epithelioid granulomas inside and adjacent to dilated lymphatic vessels. Polymerase chain reaction testing was negative for herpes simplex virus.

Conclusions: Isolated eyelid swelling that mimics thyroid-associated ophthalmopathy may occur in MRS. Computed tomography may be useful in the diagnosis. Biopsy should be performed in all cases of unexplained nonpitting eyelid edema. In the eyelid, MRS is characterized histopathologically by a granulomatous lymphangitis, a finding that seems to be unique to this condition.


ELAPSING OROFACIAL edema, recurrent facial nerve paralysis, and a fissured tongue characterize Melkersson-Rosenthal syndrome (MRS).1-3 The complete syndrome is very rare; monosymptomatic or sequential involvement is more common. Although localized orofacial swelling occurs with a prevalence of 86%, there are only 5 cases of isolated eyelid edema previously described.2,4-7 Independent of location, the edema is painless, nonpitting, and usually unilateral. After several attacks, facial enlargement may become permanent due to increasing fibrosis. The facial palsy is usually unilateral and mimics Bell palsy in time course. The facial weakness may be accompanied by disturbances in taste, hearing, or ear pain. The swelling tends to precede the palsy by months to years.1-17 The furrowed tongue (lingua plicata) is the least common finding and is not pathognomonic. We present the clinical features and histopathologic findings in 4 patients with chronic eyelid swelling.

REPORT OF CASES

CASE 1

A 33-year-old woman had an 8-year history of left-sided facial swelling that developed during her first pregnancy. Immediately postpartum, the facial swelling improved but an erythematous eruption at the left corner of her mouth became progressively swollen. The region of erythema was painless, nonpruritic, and accompanied by nonpitting edema. A similar lesion developed over the right upper lip within several months. An incisional lip biopsy specimen demonstrated nonnecrotizing granulomas, consistent with MRS. A 3-month trial of oral prednisone was ineffective. Approximately 1 year later, similar erythema and edema involving the left upper and lower eyelids developed. Oral prednisone was instituted for 1 year without clinical improvement. She was referred to our institution for further evaluation and management.

Her medical history revealed occasional left-sided headaches accompanied by hyperesthesia. She had no history of gastrointestinal, dermatologic, or rheumatologic symptoms or signs. She denied any tongue abnormalities or difficulty with speaking or swallowing. Her only medication at the time of evaluation was birth control pills. Her social history was significant for a 10-year history of 5 smoking cigarettes a day. She denied any food, drug, or environmental allergies.

On examination, nontender, nonpitting erythematous edema of the left upper and lower eyelids (Figure 1) and left...
lower lip was present (Figure 2). The skin had a peau d’orange texture. Generalized edema was present in the left cheek, creating facial asymmetry. Facial nerve function was intact and symmetric. The remainder of her ocular examination results were normal; proptosis and lagophthalmos were absent. Basal tear secretion was normal (18 and 20 mm on basic Schirmer testing). Her tongue appeared normal.

Laboratory values, including electrolytes, liver function tests, complete blood cell count, erythrocyte sedimentation rate, complement (C3, C4), antinuclear antibody, antineutrophilic cytoplasmic antibody, and angiotensin-converting enzyme, were all within normal limits. Although free thyroxine and thyroglobulin antibodies were normal, the thyroid-stimulating hormone levels were borderline low. Her chest x-ray film was normal. Both computed tomographic (CT) and magnetic resonance imaging (MRI) scans confirmed isolated left periorbital swelling. With contrast, CT demonstrated heterogeneously enhancing left eyelids (Figure 3). The osseous structures of the orbit were normal. An MRI scan of the orbits demonstrated well-defined, preseptal expansion that was mildly hyperintense on T2 images, isointense to muscle on T1 images, and enhanced somewhat heterogeneously (Figure 4). No infiltration of the adjacent fat was seen. Debulking of the left upper eyelid skin, subcutaneous tissues, and orbicularis oculi muscle was performed. The eyelid biopsy specimen showed multiple discrete, nonnecrotizing granulomas composed mostly of epithelioid cells with rare multinucleated giant cells. Many granulomas were adjacent to dilated lymphatic channels. These dilated lymphatic vessels were either empty or contained lymph and few macrophages (Figure 5 and Figure 6), or completely occluded and distended with granulomas composed of epithelioid cells (Figure 7). The granulomatous process involved the dermis and the underlying orbicularis muscle. There were scattered areas of nongranulomatous inflammation with lymphocytes, plasma cells, and mast cells.

No foreign bodies were found by polarization microscopy. Special stains for fungi (Gomori–methenamine silver), bacteria (Brown-Hopps), acid-fast bacilli (Ziehl-Nielsen), and M. leprae (Fite-Faraco) were negative. Immunohistochemical studies using monoclonal an-
tibodies for the histiocytic markers KP-1 and lysozyme were positive in the epithelioid cells. The endothelial cells lining the lumens of the lymphatic vessels stained positive for factor VIII (Figures 6 and 7). The walls of the vessel were negative for muscle actin. Analysis of the eyelid tissue with polymerase chain reaction for the DNA of herpes simplex virus 1 was negative. The lip specimen showed a similar granulomatous process. A small nerve was partially involved by granulomatous inflammation in a fashion often noted in tuberculoid leprosy. Fite-Faraco stain for *M leprae*, however, was negative.

The patient tolerated the eyelid debulking and was pleased with the improved cosmetic appearance. Although she had no history of leprosy or exposure to leprosy, our infectious disease consultant recommended a trial of the antileprosy drug clofazimine (100 mg/d for 10 days followed by 200 mg/wk). She has been clinically stable during a 2-year postoperative follow-up.

**CASE 2**

A previously healthy 47-year-old Hispanic man had a 2-month history of right periorbital swelling refractory to tobramycin-dexamethasone solution (Figure 8). Affected and efferent function were intact. Boggy edema of the right upper and lower eyelids was present without proptosis. The anterior and posterior segments were normal. Treatment with systemic antibiotics was initiated for a presumptive diagnosis of preseptal cellulitis. An orbital MRI scan showed preseptal enhancement similar to...
that in case 1 and did not demonstrate any postseptal changes. The eyelid edema did not change and the antibiotic therapy was stopped after 10 days. A 2-week course of oral prednisone was begun, with some improvement of the eyelid edema. Despite this improvement, 2.5 mm of ptosis remained. Two months later, a levator resection and debulking procedure of the skin and subcutaneous tissues of the right upper eyelid were performed.

Histopathologic examination of the tissue revealed perivascular noncaseating granulomatous inflammation involving the skin and levator muscle. There were many dilated lymphatic vessels, some of which were occluded with granulomas containing epithelioid cells (Figure 9). Polarization for birefringent foreign bodies was negative. Special stains for fungi and bacteria were negative. In light of the histopathologic suggestion of MRS, additional clinical history was sought. The patient had no history of facial or lip swelling, no history of a facial palsy, and a normal tongue. The patient also had no history of migraine headaches or gastrointestinal or dermatologic disorders.

CASE 3

A 74-year-old man had chronic edema and ptosis of the upper eyelid. A debulking procedure of the skin and subcutaneous tissues was performed. No further clinical history was available. Histopathologically, the skin and subcutaneous tissues showed similar perivascular, non-necrotizing granulomas as well as dilated lymphatic vessels, some of which contained intraluminal granulomas. Special stains for bacteria, acid-fast bacilli, and fungi were negative. Polarization revealed no birefringent foreign bodies.

CASE 4

A 74-year-old man had a 10-year history of bilateral but asymmetric upper eyelid lymphedema attributed to hypothyroidism. The patient was initially given a therapeutic dose of levothyroxine sodium without improvement of eyelid appearance. Because of the progressive nature of the eyelid deformity, the patient was finally referred to a subspecialist (Figure 10). On examination, the tissue demonstrated swelling of the subcutaneous tissue and dermal thickening not classic for blepharochalasis. On palpation, the nonpitting edema was firmer than the boggy nature of eyelid edema seen in thyroid-associated ophthalmopathy. Excisional biopsy revealed histopathology consistent with MRS, similar to the previous cases.

COMMENT

In our series, the complete clinical triad of MRS—orofacial edema, facial palsy, and furrowed tongue—was not present. Unilateral or asymmetric eyelid edema and thickening was present in all cases. One patient experienced ipsilateral facial edema that involved the lips. None of the patients had a history of facial paralysis or fissured tongue. Although eyelid edema due to MRS is an unusual entity, the clinical findings may be difficult to distinguish from blepharochalasis or thyroid-associated ophthalmopathy. Histopathologic inspection is essential for diagnosis; granulomatous inflammation with lymphangitis is diagnostic.

Computed tomographic imaging was helpful in delineating the granulomatous nature of the edema. The imaging characteristics of MRS have not been previously defined. The CT scan in case 1 demonstrated a previously undescribed heterogeneous pattern of enhancement, but the MRI revealed only nonspecific, preseptal expansion with gadolinium enhancement.

Noncaseating perivascular granulomas are an important histologic hallmark of MRS. In this series, the skin, orbicularis, and levator muscles were all involved in the disease process. Affected areas demonstrated nonspecific inflammation consisting of lymphocytes and plasma cells, or nonnecrotizing granulomas adjacent to blood vessels and lymphatic channels. In addition, we noted intraluminal granulomas in all cases. This finding has not been previously emphasized in any other condition and seems to be unique to MRS. Intravascular, but not intralymphatic, histiocytes have been found in intravascular histiocytosis, a rare hematologic
neoplasm not associated with edema.\textsuperscript{19} The granulomatous lymphangitis we observed explains the lymphedema and lymphangiectasia widely described and is a logical cause of the nonpitting edema and peau d’orange appearance seen clinically.

The recurrent facial edema of MRS resembles angioneurotic edema in the acute phase. However, as the relapses become more frequent and the edema more chronic, the 2 major entities in the differential diagnosis are blepharochalasis and thyroid-associated ophthalmopathy (Table). Blepharochalasis is characterized by remitting and relapsing bilateral eyelid edema. The skin of the eyelids is typically thin, with a bronze discoloration, and wrinkled in a “cigarette paper” pattern.\textsuperscript{20} On histopathologic inspection, atrophy of all dermal layers is accompanied by a nonspecific cellular infiltrate. In thyroid-associated ophthalmopathy, eyelid retraction, lagophthalmos, or injection over the rectus muscles often accompanies bilateral eyelid edema. The skin may be erythematous, but is not thickened. There is no surface pattern of distinctive wrinkling. Lacrimal gland prolapase is common and there is a palpable accumulation of fluid in the subcutaneous tissues. Histologically, a chronic cellular infiltrate accompanies subdermal edema.\textsuperscript{21}

The cause and pathogenesis of MRS is unknown; chronic infection, hypersensitivity to bacteria, dental granulomas, allergy, and genetic predisposition have all been suggested.\textsuperscript{1,2,22-26} An allergen has never been identified and eosinophilia does not occur.\textsuperscript{2} Environmental factors have been implicated, but removing the offending agent does not consistently result in remission.\textsuperscript{17,22,23} Alexander and James\textsuperscript{2} reported a viral prodrôme in 22\% of patients. Vesicular lesions of the lips and oral mucosa suggestive of herpes simplex have been noted in association with MRS.\textsuperscript{2,27} In addition, the swelling of MRS has been reported to present and then recur or worsen during stress. Vesicular lesions and histologic nerve involvement as seen in case 1 may occur with herpes simplex infection, but polymerase chain reaction for the genomic sequences of herpes simplex virus 1 was negative.

The management of MRS is challenging. Corticosteroids have been tried topically, intralesionally (2-3 mg of triamcinolone suspension weekly for 5-8 months), and systemically.\textsuperscript{5} A variety of drugs have also been used (dapsone, clofazimine, sulfasalazine, hydroxychloroquine, penicillin, tetracycline, erythromycin, clindamycin, ranitidine, diphenhydramine) without reproducible improvement.\textsuperscript{1,8,27-30} As a result of reported angiotensin-converting enzyme elevation and the sarcoidlike appearance of granulomas on histopathologic inspection, trials of corticosteroids, tetracycline, and methotrexate were initiated in selected patients and demonstrated some success.\textsuperscript{31} The antilepromatous agent clofamazimine (100 mg daily for 10 days, then 200-400 mg weekly) has also been reported to reduce swelling and resolve granulomas by an unknown mechanism.\textsuperscript{29} Focal external beam irradiation has also been tried without definitive benefit.\textsuperscript{7} A combination of surgical debulking and intralesional steroid therapy has been advocated to improve cosmesis.\textsuperscript{1,32} Recurrent intralesional therapy delivered weekly for the first 2 months and then tapered during the next 6 months has also been advocated.\textsuperscript{6,30} Surgical management has included reduction cheiloplasty and reduction blepharoplasty to debulk facial swelling when the swelling has stabilized.\textsuperscript{32} Facial nerve decompression has been successful when facial paralysis persisted or recurred frequently.\textsuperscript{8,13,33} The effectiveness of any intervention are difficult to determine because remission and relapse are common. No individual or combination therapy results in complete remission.

### Table: Differential Characteristics of Isolated Chronic Eyelid Edema

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Female-Male Ratio</th>
<th>Age Range, y</th>
<th>Eyelid Skin</th>
<th>Laterality</th>
<th>Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melkersson-Rosenthal syndrome</td>
<td>2:1</td>
<td>20-30</td>
<td>Thickened, erythematous vesicles possible, peau d’orange edema, erythema</td>
<td>Unilateral</td>
<td>Facial edema, facial nerve palsy</td>
</tr>
<tr>
<td>Thyroid-associated ophthalmopathy</td>
<td>3:1</td>
<td>40-60</td>
<td>Subdermal edema, erythema</td>
<td>Bilateral</td>
<td>Lagophthalmos, eyelid retraction, proptosis, chemosis, lacrimal prolapse</td>
</tr>
<tr>
<td>Blepharochalasis</td>
<td>1:1</td>
<td>20-30</td>
<td>Thin, erythematous, “cigarette paper,” bronze coloration</td>
<td>Bilateral</td>
<td>Fat atrophy, pseudoepicanthal fold, lacrimal prolapse</td>
</tr>
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</table>

This case series presents 3 new findings regarding MRS. First, we emphasize monosymptomatic eyelid presentation and stress the need for biopsy to distinguish this condition from blepharochalasis and thyroid-associated ophthalmopathy. Second, we characterize the radiological appearance of the eyelid edema on CT and MRI and note that CT is superior in depicting the heterogeneous pattern of inflammation analogous to the granulomas seen histopathologically. Finally, we expand the histopathologic features of this entity. In all 4 cases, the unique observation of granulomas within the lymphatic vessels was documented; all previous studies reported granulomas surrounding the lymphatic vessels. Furthermore, we postulate that this process may account for the dilated lymphatic vessels and the corresponding characteristic eyelid edema. We report for the first time molecular analysis of the tissue for herpes simplex virus, a frequently mentioned possible etiologic factor. Melkerson-Rosenthal syndrome should be considered in all cases of isolated eyelid edema and a diagnostic incisional biopsy should be performed. Histologically, the presence of perilymphatic granuloma, granulomatous lymphangitis, and lymphedema are characteristic features of this syndrome.
REFERENCES


