

## Grand Rounds

### A 49-year-old man with unilateral, nontender left eyelid swelling

Brandon J. Wong, BA,<sup>a</sup> Bryan K. Hong, MD,<sup>b</sup> Daman Samrao, MD,<sup>c</sup> Gene H. Kim, MD,<sup>c</sup> and Narsing A. Rao, MD<sup>b</sup>

Author affiliations: <sup>a</sup>Keck School of Medicine, University of Southern California, Los Angeles, California;

<sup>b</sup>Doheny Eye Institute, Keck School of Medicine, University of Southern California, Los Angeles, California;

<sup>c</sup>Department of Dermatology, Keck School of Medicine, University of Southern California, Los Angeles, California

## History

A 49-year-old Hispanic man presented to the Los Angeles County Hospital Ophthalmology clinic with a nontender, left upper eyelid swelling of 14 months' duration (Figure 1). On two occasions, his eyelid had been lanced at an outside ophthalmology clinic and yielded a "dark, reddish-brown liquid," which did not grow any organisms on bacterial culture. According to the patient, the edema improved for 3 days after lancing and then recurred. A 3-week course of oral phenylephrine hydrochloride 20 mg/chlorpheniramine maleate 4 mg and a 4-week trial of sulfamethoxazole/trimethoprim double strength 500 mg twice daily prescribed by the patient's referring doctor had no effect. The apparent cellulitis, which had slowly worsened over a month then stabilized in character for more than a year, led to the patient's loss of employment and further rendered him unable to obtain work in the food industry due to concerns over his appearance. The patient denied any eye pain or changes in his vision, including loss of vision or diplopia. He had no other systemic symptoms and denied any facial muscle weakness.

Past medical and surgical history were unremarkable. Other than the 2 previous eyelid lancements, the patient denied any other eyelid surgery, injectables, or ocular history. The patient was not on any medications. Family and social history were noncontributory.

## Examination

On clinical examination, the patient's best-corrected visual acuity was 20/20 in the right eye and 20/30 in the left eye. Intraocular pressure by applanation was 17 mm



**Figure 1.** A 49-year-old man with left upper eyelid swelling of 14 months' duration at presentation.

Hg in each eye. Ductions were full, and versions were comitant. Pupils were equal, round, and reactive to light. There was no afferent pupillary defect. Ptosis evaluation was performed bilaterally: the right eye had a palpebral fissure of 9 mm, a margin reflex distance 1 of 4 mm, levator function of 15 mm, no lagophthalmos, and a normal eyelid, while the left eye had palpebral fissure of 7 mm, a margin reflex distance 1 of 2 mm, levator function of 14 mm, no lagophthalmos, and painless, nonpitting edema of the left upper eyelid, with no warmth or erythema. There were no palpable orbital masses and no resistance to retropulsion. Hertel exophthalmometry findings were normal, with 19 mm of protrusion bilaterally. Slit-lamp examination and dilated fundus examination were normal bilaterally, with no palpebral conjunctival follicles or lacrimal gland enlargement. Other than the isolated left eyelid swelling, the face was symmetrical, and there was no evidence of other facial swelling. The patient had normal facial motor movement with no signs of weakness or paralysis. In addition, the patient had a relatively normal tongue on examination, with only a minor, centrally located fissure (Figure 2).

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Correspondence: Brandon Wong, Keck School of Medicine of the University of Southern California, 1975 Zonal Ave, Los Angeles, CA 90089 (email: brandojw@usc.edu).



**Figure 2.** Patient at presentation with relatively normal tongue, with only a mild fissure located centrally (arrow).

## Ancillary Testing

Laboratory testing revealed a normal complete blood count, metabolic panel, thyroid stimulating hormone, thyroid-stimulating immunoglobulin index, C1 inhibitor function and C4 levels, erythrocyte sedimentation rate, and C-reactive protein. It also showed negative antinuclear antibody, rheumatoid factor, Lyme serology, HIV 1 and 2, and tuberculin skin tests.

## Treatment

The patient was started on systemic corticosteroid therapy with a plan to taper his therapy over a 4-week period. He is continuing to be followed for further monitoring of his eyelid edema.

## Differential Diagnosis

Because of the nonspecific appearance of the eyelid edema, the initial differential diagnosis was very broad, encompassing infection, thyroid orbitopathy, blepharochalasis, angioedema, lymphedema, allergic or contact dermatitis, eyelid malignancy, periorbital pseudotumor, ocular rosacea, and eosinophilic granuloma.

Eyelid infections, such as periorbital or orbital cellulitis, may present with eyelid edema. Periorbital infections are preseptal and can be caused by trauma, bacteremia, or upper respiratory illnesses. Patients experience eyelid induration, erythema, and tenderness. Orbital cellulitis involves the orbit itself; symptoms are severe, including proptosis, pain on eye movement, ophthalmoplegia with diplopia, and decreased visual acuity. A diagnosis of periorbital or orbital cellulitis can be made based on history and physical examination, although computed

tomography or magnetic resonance imaging can be helpful in evaluating for orbital cellulitis and its complications.

Thyroid orbitopathy can cause chronic eyelid edema, although it is usually bilateral and occurs in older individuals (40–60 years of age). It is associated with lagophthalmos, eyelid retraction, and proptosis. It can be excluded by laboratory tests and orbital imaging studies.

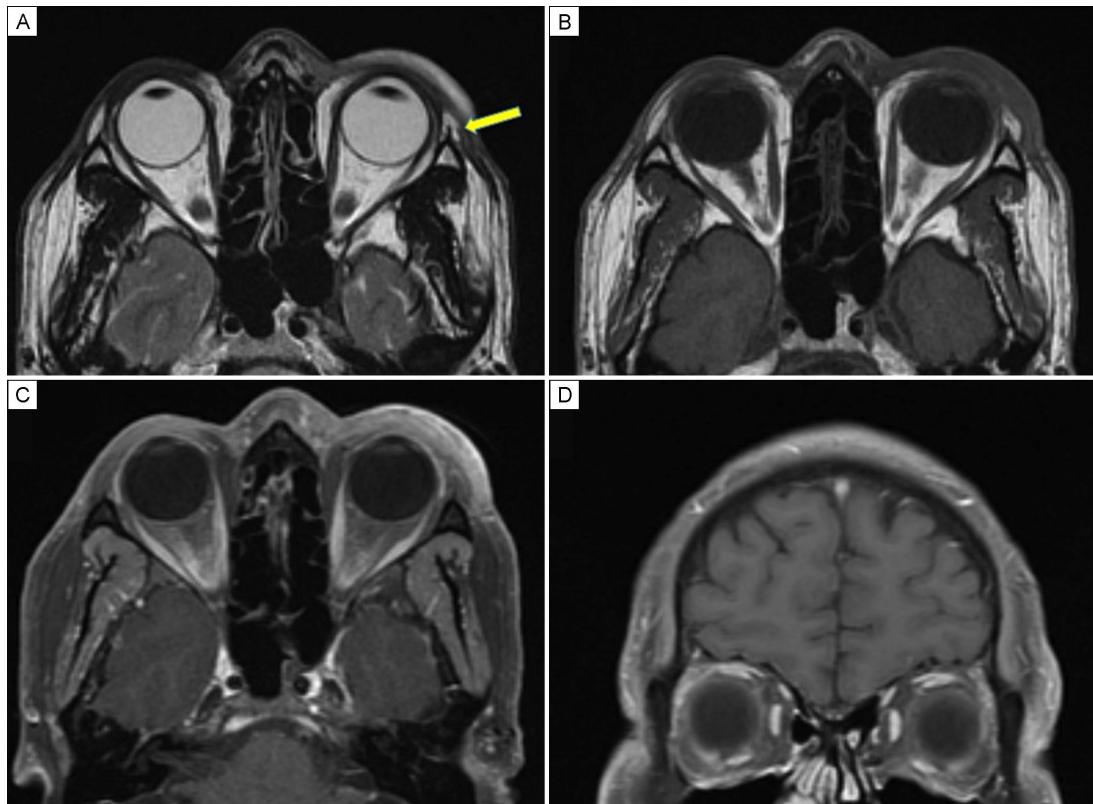
Blepharochalasis can also present with eyelid edema that is usually bilateral, although it can occur unilaterally. It is characterized by recurrent episodes of nonpainful, nonerythematous upper eyelid swelling that usually begins in childhood or adolescence. These episodes last an average of 2 days, but recurrent episodes can cause the eyelids to become discolored, thin, and wrinkled, with the classic appearance of tissue paper. These episodes have been noted to decrease in frequency as patients age. Treatment is primary surgical and aims to restore function and maintain cosmesis.<sup>1</sup>

Angioedema can be hereditary or acquired. Hereditary angioedema can be detected with laboratory testing for C1 inhibitor protein and complement C4 levels. The acquired form is often caused by an immunologic response to an allergen and may occur with other allergy symptoms. Angioedema due to an allergen usually responds to treatment with antihistamines or steroids.

Lymphedema is usually the result of invasive surgical procedures that result in lymphoceles or lymph fistulas, which are most commonly described in vascular procedures involving the lower extremities. Lymphorrhea is usually a clear, amber-colored fluid unlike the dark fluid seen in our patient.

Allergic or contact dermatitis could also present with eyelid swelling. This hypersensitivity reaction can occur with a variety of allergens, and patients present with pruritus and inflammation at the affected site. A unilateral presentation would be uncommon, and our patient did not identify any unusual contacts to precipitate an allergic response. Diagnosis can be made clinically, with an emphasis on a detailed history, and is confirmed by patch testing.

Eyelid malignancies, periorbital pseudotumor, and eosinophilic granulomas may be diagnosed by biopsy. Patients with ocular rosacea may present with associated skin findings, including rhinophyma, pustules, papules, and erythema.



**Figure 3.** Magnetic resonance imaging of the orbits obtained in sequence. A, Axial T2-weighted imaging before contrast showing left eyelid soft tissue swelling and no evidence of lacrimal gland enlargement (yellow arrow). B, Axial T1-weighted imaging before contrast showing left eyelid soft tissue swelling. C, Axial T1-weighted imaging after contrast with fat suppression showing continued left eyelid soft tissue swelling and no focal areas of enhancement. D, Coronal T1-weighted imaging after contrast with fat suppression showing no extraorbital masses or abnormal enlargement of extraocular muscles.

## Diagnosis and Discussion

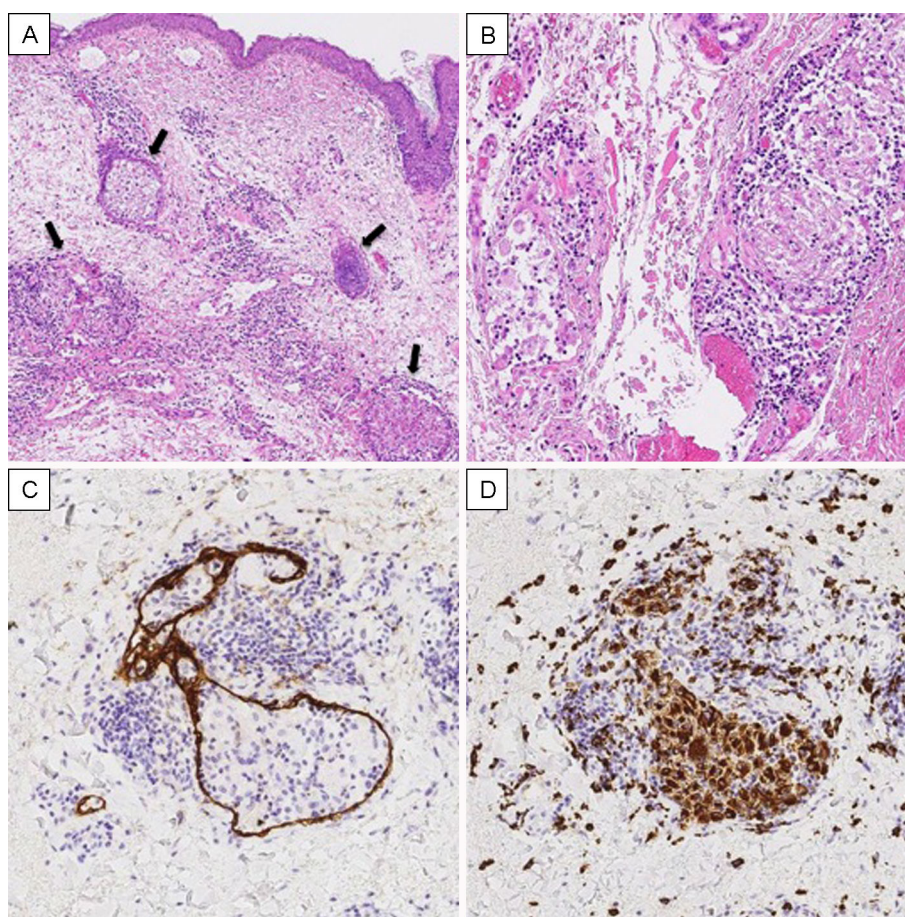
Given the chronicity of the eyelid edema and lack of response to oral phenylephrine/chlorpheniramine, magnetic resonance imaging (MRI) of the orbits with and without contrast was obtained. The MRI showed globes normal in size, shape, and intensity, with no evidence of intra- or extraconal soft tissue masses and no focal areas of enhancement after contrast. Left periorbital edema consistent with soft-tissue swelling was noted (Figure 3).

The MRI results, combined with a negative laboratory work-up for other possible causes of eyelid edema and questionable tongue abnormality, led to a diagnostic biopsy of the upper left eyelid. A full thickness biopsy, including skin and orbicularis oculi, was taken from the space between the lid crease and the brow, yielding a  $3.5 \times 1.0 \times 0.1$  cm tissue specimen. Histopathologic evaluation of the specimen showed diffuse edema of the superficial dermis accompanied by ectatic lymphatics and

loosely formed, noncaseating granulomas, many of which appeared to be within the lumens of lymphatics or vessels (Figure 4). All stains, including Gram stain, and special stains for microorganisms (Periodic acid-Schiff and acid-fast bacilli) were negative, and no polarizable foreign material was identified. No eosinophils were noted. Immunohistochemical staining with D2-40 and CD68 confirmed the presence of ectatic lymphatics and intralymphatic histiocytosis. Based on the clinical symptoms, combined with the histopathologic results, a diagnosis of Melkersson-Rosenthal syndrome was made.

Melkersson-Rosenthal syndrome (MRS) is classically described as a triad of recurrent facial paralysis, orofacial edema, and fissuring of the tongue (lingua plicata).<sup>2</sup> The dominant feature of the syndrome is orofacial edema, which is painless, nonpitting, unilateral, and typically includes the eyelids and lips.<sup>3</sup> The facial paralysis can be unilateral (mimicking Bell's palsy) or bilateral.<sup>4</sup> Lingua plicata is the rarest component of the triad and is not considered pathognomonic of the disease. Patients





**Figure 4.** A, A low-power photomicrograph showing dermal edema, dilated lymphatics and noncaseating granulomas (black arrows) associated with the lymphovascularity along with an infiltrate of chronic inflammatory cells (hematoxylin and eosin, original magnification  $\times 10$ ). B, High-power image of the granulomas showing a loose collection of histiocytes possibly within the lumen of a lymphatic or vessel. Chronic inflammation is present surrounding the granulomas (hematoxylin and eosin, original magnification  $\times 20$ ). C, The D2-40 stain highlights the presence of a lymphatic wall surrounding a loosely formed granuloma. D, The presence of the intralymphatic granuloma is confirmed by the CD68 stain.

may be mono- or oligo-symptomatic, and in such cases the presence of only one or two features in the triad can make this a challenging diagnosis. Moreover, the features may present over a period of years, which further complicates the diagnosis.<sup>5</sup> The etiology of the syndrome remains unclear, though autoimmune or viral causes have been hypothesized.<sup>3,6</sup> Symptoms tend to present around the second or third decade of life, although infrequently they can present in childhood or after 50 years of age.<sup>7</sup> Studies regarding the gender predisposition for the syndrome are conflicting, with females being equally or slightly more affected than males.<sup>3,8</sup>

Our patient did not manifest the classic triad of Melkersson-Rosenthal syndrome, presenting only with isolated left upper eyelid edema and no clinical evidence of

facial nerve paralysis or gross lingua plicata. A diagnosis of MRS requires a high index of clinical suspicion as well as histopathological evidence for confirmation of the diagnosis. The distinctive histopathology of MRS is described as non-caseating, granulomatous lymphangitis with granulomas within and around the lymphatics and blood.<sup>3,4,8</sup> MRS should be considered in patients presenting with eyelid edema of unknown etiology and biopsy should be performed.<sup>9</sup>

Initial treatment for Melkersson-Rosenthal syndrome usually consists of topical, intralesional, or systemic corticosteroid therapy, although the syndrome is often refractory to treatment. Patients with MRS are also treated with nonsteroidal, anti-inflammatory drugs such as metronidazole, dapsone, acyclovir, methotrexate, and thalidomide, with varying levels of response.<sup>5</sup> Clofazi-

mine, an anti-lepromatous drug, has also been reported to decrease some of the eyelid swelling and associated granulomas.<sup>10</sup>

Surgical management of eyelid edema, such as debulking procedures or blepharoplasty, may be indicated if the edema is unresponsive to steroids, if it becomes visually significant, or becomes cosmetically unacceptable for the patient.<sup>11</sup>

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