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The authors have no financial or conflicts of interest to disclose.

The manuscript has been read and approved by both the authors.

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Transient Eyelid Edema Following COVID-19 Vaccination

To the Editor:

Vaccinations have provided immunological protection against pathogens for nearly 100 years and while uncommon, complications of the eyes and ocular adnexa can occur with varied presentation.[1] Anaphylactic reactions are known to present with ocular symptoms, such as eyelid puffiness, but are typically accompanied by systemic inflammatory symptoms.[1] Separately, several vaccines are known to cause adverse eyelid effects that are distinct from anaphylactic reactions. Periorbital swelling with ocular vaccinia is a known complication of the smallpox vaccine, with 3.6 per 100,000 vaccines presenting with periorbital edema.[2] Additionally, transient eyelid edema as a symptom of ocular respiratory syndrome was reported with the influenza vaccine in the early 2000s.[3] Studies demonstrated that the peak incidence of ocular respiratory syndrome was 46 per 100,000 patients and of those, 18% presented with edema, primarily of the eyelid.[3]

The Pfizer-BioNTech COVID-19 vaccine was issued an emergency use authorization on December 11, 2020.[4] It has been demonstrated to have a 95% efficacy following the second dose.[4] However, adverse reactions have been reported. In a review of the Vaccine Adverse Events Reporting System data, it was found that isolated ocular reactions to the COVID-19 vaccine are uncommon, with only 46 reported cases, and of those, 34 (74%) are associated with the eyelid.[1] We describe a series of 3 female patients who presented with spontaneous unilateral eyelid edema and erythema with otherwise normal ocular exams following administration of the Pfizer COVID-19 vaccine.

In our 3 patients, average age was 39.3 years old (range: 32–43 years), and all patients had no ocular or medical history. They each presented on day 1 or 2 following their first or second dose of the Pfizer COVID-19 vaccine. Each patient presented with unilateral upper greater than lower eyelid edema and erythema without other associated ocular, adnexal, or systemic findings (Fig.). The 3 patients were treated with observation, antihistamines, and oral steroids, respectively, and each patient had full resolution of their symptoms in 1–2 days without sequela.

We acknowledge that the precise etiology and pathophysiology of these patients' spontaneous eyelid edema is unknown and cannot be definitively associated with the COVID-19 vaccination. However, there are proposed immunologic mechanisms for adverse vaccine-related events, including complement system activation and molecular mimicry.[5] In normal immunology, the complement system within tear film is an important part of the closed eye's immunological defense, and its activation results in an increase in cytokine inflammatory mediators.[6] It has been suggested that complement mediators in the tear film are the result of the leakage of plasma.[6] Studies have demonstrated that the complement system has a critical role in the pathogenicity of COVID-19.[7] In our patients, it is possible that the COVID-19 vaccine caused complement activation that increased complement mediators within the plasma and tear film, resulting in eyelid edema.

Alternatively, the COVID 19 vaccine may trigger a specific immune response pathway through molecular mimicry. There are a number of SARS-CoV-2 proteins that exhibit cross reactivity with human proteins and could result in autoimmunity.[7] However, it is not plausible that an adaptive cross-reactive immune response to SARS-CoV-2 spike protein receptor-binding domain could be manifest as soon as 1 day after administration of mRNA encoding it. It has also been suggested that antibodies to the spike glycoprotein of the mRNA vaccines can elicit an acute autoimmune response.[7] Specific stimuli that initiate reactivation of autoimmune responses in diseases such as thyroid eye disease have not been identified, and it has been suggested that molecular mimicry has a role in the development of such diseases.[8] We hypothesize that the patients' eyelid edema is the result of a reactivation of an autoimmune response that is triggered by the mRNA vaccine.

These 3 cases may represent a relatively uncommon reaction related to the vaccine that was either self-limited or resolved with minimal treatment. In similar cases, appropriate workup should be performed to rule out masquerading entities, but it may assist the clinician to appreciate this potentially self-limited, vaccine-related entity in the appropriate context. To our knowledge, this is the first report of unilateral, spontaneous eyelid edema following vaccination with the Pfizer COVID 19 mRNA vaccine. It is important for the ophthalmologic and medical community to be aware that such ocular reactions do occur

Figure. Mild, unilateral, upper greater than lower, eyelid erythema, and edema presenting 1 day after the first dose of the SARS-CoV-2 Pfizer mRNA Vaccination. No additional ocular or adnexal signs or symptoms were observed. This patient's eyelid edema and erythema resolved in 1 day with antihistamine treatment and the patient experienced no known ocular sequela.

and future studies with adequate powering should be performed to further characterize and understand this process.

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The authors have no financial or conflicts of interest to disclose.

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Radiological Features of Small Lymphocytic Lymphoma Involving the Lacrimal Sac

To the Editor:

We report a case of small lymphocytic lymphoma (SLL) involving the lacrimal sac and highlight the unique radiological features. This letter adheres to the tenets of the Declaration of Helsinki.

A 71-year-old man with a background of stage IIIA SLL, hypertension, hypercholesterolemia, and previous thromboembolic stroke presented with 5 days of progressive left periorbital swelling and upper eyelid ptosis which was unresponsive to oral antibiotic therapy. Examination revealed visual acuity of 20/25 OU with left periorbital edema, proptosis, near complete ophthalmoplegia, but no optic neuropathy.

MRI of the orbits (Fig. 1) revealed bilateral lacrimal sac masses with a homogeneous isointense T1 signal and well-delineated isointense sac wall thickening on T2 sequences. The intrasac contents had relatively low enhancement. A high diffusion-weighted imaging signal combined with hypoenhancement on apparent diffusion coefficient sequences was indicative of restricted diffusion. The discrepancy between a unilateral acute episode and radiological evidence of bilateral lacrimal sac involvement suggested a possible systemic process. Given our patient's past medical history and the presence of restricted diffusion on MRI, there was a strong clinical suspicion for lymphomatous infiltration of the lacrimal sac with superimposed infection.

The patient was admitted for presumed orbital cellulitis and treated with intravenous cefazolin and flucloxacillin. His periorbital edema and ocular motility normalized within several days except for a residual left medial canthal mass. A left endonasal dacryocystorhinostomy performed 3 weeks later revealed edematous nasal mucosa and a pale lacrimal sac with thickened irregular folds (Fig. 2). Biopsies from the nasal mucosa and posterior lacrimal sac were sent for histopathology and flow cytometry analysis. This demonstrated dense small lymphoid infiltrates consistent with SLL, with coexpression for CD20 and CD5. The patient was referred to his hematologist for consideration of systemic treatment.

Lacrimal sac lymphomas are rare and represent 2–6% of all lacrimal sac malignancies.[1,2] The most common subtypes, whether primary localized or secondary to systemic disease, are high-grade diffuse large B-cell lymphoma, mucosa-associated lymphoid tissue lymphoma, and unclassified B-cell lymphoma.[2,3] Lacrimal sac SLL tumors are more likely to arise from systemic disease (12% systemic SLL compare 3% primary localized SLL), as was seen in our patient.[3,4] The onset of lacrimal sac involvement in SLL is reported to range from 14 months to 8 years after a systemic diagnosis.[4]

On MRI, lacrimal sac lymphoma is characterized as an infiltrative mass with isointense to hyperintense T1 and T2 signals.[3,5,6] These findings have been described in diffuse large B-cell lymphoma, mucosa-associated lymphoid tissue lymphoma, mantle cell lymphoma, and follicular lymphoma subtypes.[3,5–8] Our case of bilateral lacrimal sac SLL involvement exhibited a homogeneous isointense T1 signal. T2-weighted images were useful for delineating an isointense thickening of the sac wall with relatively hyperintense intrasac contents. Thickening of the sac wall and intrasac opacification have also been reported in mantle cell lymphoma.[9] The extent of contrast enhancement in lacrimal sac lymphoma is inconsistent, likely because of the variable proportion of tumor cells and interstitial tissue.[7] In our patient, the combination of a high diffusion-weighted imaging signal with low apparent diffusion coefficient enhancement of the bilateral lacrimal sac masses was indicative of restricted diffusion, which is consistent with hypercellular contents secondary to a lymphoproliferative disorder.[10]

A differential diagnosis in this case was chronic dacryocystitis with bilateral mucoceles. Clinically, a lacrimal sac mucocele can mimic lymphoma and present as a non-reducible medial canthal mass.[11] On MRI, mucoceles create a cystic dilatation of the lacrimal sac with rim enhancement demonstrating a thin sac wall, which is distinct from lymphomatous sac wall thickening.[12] Furthermore, inflammatory dacryocystitis and mucoceles are more likely to exhibit strong hyperintense T2 signals compared with neoplastic lesions.[2]