Orbital myositis and scleritis after anti-SARS-CoV-2 mRNA vaccines: A report of three cases

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Abstract

Purpose: To report three cases of ocular myositis and scleritis, bilateral scleritis and unilateral single muscle myositis after mRNA COVID-19 vaccination.

Methods: Case series of three patients who presented to the Orbit Outpatient Service of Fondazione Polyclinico Universitario A. Gemelli with a history of unilateral proptosis, diplopia and pain, bilateral red eye and pain during eye movements and unilateral proptosis and inconstant diplopia respectively with onset 5–10 days after m-RNA COVID-19 vaccine. A thorough hematologic work up and orbital contrast enhanced magnetic resonance imaging (MRI) in patients with proptosis was performed.

Results: Patients were females, 64, 58 and 45 years old respectively. MRI showed enlargement of all right rectus muscles, with both muscle belly and insertion involvement in the first case associated to right scleritis. A bilateral scleritis was diagnosed in the second patient and a single muscle myositis in the third patient. Serological tests excluded thyroid disease. The first and second patient were treated respectively with oral and topical glucorticoids with a complete clinical response. Two 2 cycles of oral non-steroidal anti-inflammatory drugs were administered to the third patient with a partial response.

Conclusion: As far as we know these are the first report of orbital myositis and scleritis presenting after mRNA BNT162b2 vaccine (Pfizer/BioNTech) and mRNA-1273-(Moderna) vaccine, an uncommon effect of a likely autoimmune reaction triggered by the virus antigen.

Keywords
mRNA BNT162b2 vaccine ophthalmic adverse reactions, mRNA-1273-vaccine ophthalmic adverse reactions, orbital myositis, ocular scleritis, COVID, coronavirus

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Introduction

Orbital myositis (OM) is the most common cause of extraocular muscle disease after thyroid-associated orbitopathy (TAO). Nevertheless, is a rare disease whose pathogenesis has not yet been fully elucidated. Idiopathic OM is the most common form presenting with unilateral acute painful diplopia and often characterized by the involvement of a single muscle. However, OM associated with systemic inflammatory disease, is most commonly characterized by the involvement of more than one extraocular muscle and has been reported in cases of immunoglobulin G4-related disease, inflammatory bowel disease (IBD),

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Systemic Lupus Erythematosus (SLE), sarcoidosis, rheumatoid arthritis (RA) and antineutrophil cytoplasmic antibodies (ANCA)-related vasculitis such as Churg-Strauss syndrome and Wegner granulomatosis. Although rarely, OM has also been reported in infectious conditions such as herpes zoster ophthalmicus (HZO), Lyme disease and cysticercosis. After coronavirus disease pandemic rare cases of OM related to COVID-19 infection have been reported. Other atypical presentation of OM are cases occurring after shingles and H1N1 influenza vaccine. Ocular adverse events of COVID-19 vaccinations reported in literature include cranial nerve palsy, maculopathies, new-onset or reactivation of uveitis and new-onset Graves Disease. Few cases of scleritis have been reported in literature occurring during COVID-19 disease. Pichi et al reported cases of episcleritis and scleritis occurring after inactivated COVID-19 vaccine. We report a case series of three patients who presented unilateral ocular myositis and scleritis, bilateral scleritis and unilateral single muscle myositis, respectively, 5–10 days after mRNA COVID-19 vaccination. As far as we know these are the first cases reported in literature of orbital myositis and scleritis presenting after mRNA BNT162b2 vaccine (Pfizer/BioNTech) and mRNA-1273-(Moderna) vaccine.

### Cases description

#### Case 1

A 64-year-old woman, affected by ANCA-related vasculitis, presented to our outpatients Orbit Clinic with a 4-day history of right progressive periorbital swelling associated with redness of the eye. She complained of horizontal and vertical diplopia, pain at right eye movement without systemic symptoms. The patient reported mRNA BNT162b2 COVID-19 vaccine (Pfizer/BioNTech) 2-dose 5 days before the occurrence of the symptoms. On examination, best-corrected visual acuity was 20/20 in both eyes. No afferent pupillary defect was observed. Intraocular pressure was 11 mmHg in each eye. There was a moderate right periorbital edema, ptosis, proptosis and motility showed right upgaze limitation. Slit-lamp examination revealed chemosis and injection of the conjunctiva and episclera and scleral injection. The result of the phenylephrine test was positive for the diagnosis of scleritis. Congestion of the deep episcleral vessels remained after the application of 10% phenylephrine drops. No other signs of inflammation were found in the anterior chamber. Fundus examination revealed a normal posterior pole. Head and neck examination showed latero-cervical lymphadenopathy. Immunologic and serologic analysis excluded autoimmune disorders and thyroid disease. The patient was treated with topical dexamethasone (1 drop 6 times/day). A rapid clinical improvement was evident 4 days later of signs and symptoms after 8 days after (Figure 2).

#### Case 2

A 58-year-old woman, affected by latex allergy, was referred to our Orbit Clinic with a history of bilateral red eye, painful during eye movement, swelling of latero-cervical lymph nodes and fever. The patient had a history of Hashimoto thyroiditis but she was, at the moment, in a euthyroid phase with thyroid-stimulating hormone (TSH) level and thyroid hormone levels within the normal range. She was administered the second dose of mRNA BNT162b2 COVID-19 vaccine under intravenous anti-histaminic coverage. On examination, best-corrected visual acuity was 20/20 in the right eye and 20/20 in the left eye. No afferent pupillary defect was observed. Intraocular pressure was 16 mmHg in the right eye and 15 mmHg in the left eye. Slit-lamp examination showed a diffuse scleral hyperemia in both eyes. The result of the phenylephrine test was positive for the diagnosis of scleritis. Congestion of the deep episcleral vessels remained after the application of 10% phenylephrine drops. No other signs of inflammation were found in the anterior chamber. Fundus examination revealed a normal posterior pole. Head and neck examination showed latero-cervical lymphadenopathy. Immunologic and serologic analysis excluded autoimmune disorders and thyroid disease. The patient was treated with topical dexamethasone (1 drop 6 times/day). A rapid clinical improvement was evident 4 days later of signs and symptoms after 8 days after (Figure 2).

#### Case 3

A 45-year-old woman, healthy, with no history of systemic disease, no prior treatments, and no history of trauma was referred to our Orbit Clinic with a 3-month history of left eye proptosis occurring 6 days after the first dose of mRNA COVID-19 vaccine. She complained of inconstant right lateral gaze diplopia, left orbital pain and asthenopia while reading (Figure 3). On examination, best-corrected visual acuity was 20/20 in both eyes. No afferent pupillary defect was observed, intraocular pressure was within normal ranges and fundus examination was unremarkable. Ocular motility showed mild right-gaze limitation of left eye and a mild proptosis of the left eye was assessed. Orbital magnetic resonance imaging (MRI) showed left moderate proptosis and mild enlargement of the left medial rectus muscle, with belly involvement, without contrast enhancement. (Figure 3) Complete blood cell count, angiotensin-converting enzyme, c-reactive protein, rheumatoid factor, anti-neutrophil cytoplasmic antibodies

days of the steroid regime a significant improvement was noticed. The oral prednisone therapy was tapered by 15 mg weekly and a complete clinical response was achieved without relapse after 6 months.
(c-ANCA, p-ANCA), PR3, FT4, TSH, TRab, and serum IgG4 levels were normal.

The patient was treated with 2 cycles of oral non-steroidal anti-inflammatory drugs and at a follow-up of 3 months, reported improvement of pain and diplopia but no change in the proptosis.

**Discussion**

Cases of episcleritis and scleritis occurring during COVID-19 infection have already been reported in literature.\(^8\)\(^{-}\)\(^{10}\) Likewise, other cases have been reported recently by Pichi et al occurring after inactivated COVID-19 vaccination. The timing of onset of clinical manifestations in the cases described by us is in agreement with the timing (1 to 10 days after vaccination) reported by the authors.\(^{11}\) Moreover, as already described, the signs and symptoms improved after CS therapy.

Lacey et al. analyzed 1849 cases and reported that 95% were due to TAO, while only 5% were associated with other causes, with inflammatory conditions being the main cause of non-thyroid extraocular muscles enlargement, followed by vascular processes.\(^{12}\) Other authors reported that extraocular muscles enlargement is suggestive of
inflammatory diseases when associated with orbital and eye movement pain and painful diplopia.\textsuperscript{13,14} The Magnetic Resonance Imaging features of myositis are: involvement of belly and insertion, hypointense on T1-weighted sequences and iso-hyperintense on T2-weighted images, with variable contrast enhancement and high apparent diffusion coefficient (ADC) values on Diffusion weighted Imaging (DWI) images. The etiology of orbital myositis is still unknown. Several autoimmune disorders such as systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), sarcoidosis and ANCA-related vasculitis have been linked to this clinical entity.\textsuperscript{1} Furthermore, there are few cases reported in literature in which infection has been considered a trigger for orbital myositis. The cases reported in literature are related to herpes zoster ophthalmicus, lyme disease and, less often, retina involvement.\textsuperscript{15,16} Rare orbital manifestations suspected to be related to COVID-19 infection have been reported too.\textsuperscript{2} In two cases of orbital cellulitis occurring in young adults tested positive for COVID-19 the authors hypothesized that the alteration of muco-ciliary clearance related to the disease and the secondary bacterial infection were the cause of the cellulitis rather than the virus itself.\textsuperscript{17} Martinez-Diaz et al. reported one case of inflammatory dacryoadenitis in a young patient not responding to antibiotic therapy Conversely improving after systemic corticosteroids highlighting an immune mechanism.\textsuperscript{18} Dinkin and colleagues described one case of peri-neuritis and surrounding intraconal orbital fat inflammation.\textsuperscript{19} Cases of development of myositis in location other than the orbit have been reported as a result of COVID-19 infection. The possible mechanism hypothesized is an immune-mediated mechanism triggered by the virus. The virus needs to bind angiotensin-converting enzyme 2 (ACE2) to enter the cells. After the appearance of ACE2 epitopes autoantibodies can develop activating the autoimmune response.\textsuperscript{20} Three cases of unilateral orbital myositis in COVID-19 patients have been reported in literature. The first case was an orbital myositis occurring in a 44 years-old patient after 2 days from COVID-19 diagnosis. He developed proptosis and periorbital erythema, abduction deficits with improvement of symptoms after intravenous CS. Considering the MRI appearance, the lack of history of penetrating trauma or paranasal involvement and the improvement after intravenous corticosteroids an inflammatory etiology was suspected.\textsuperscript{3} The other reported cases were all characterized by unilateral OM occurring in young patients affected by a mild form of COVID-19 and improving after

**Figure 3.** (A) clinical appearance showing left proptosis and slight right gaze limitation. (B) and (C) post contrast T1-weighted orbital magnetic resonance images showing left-sided moderate proptosis, moderate enlargement of medial rectus muscle (belly). (D and E): T2-weighted Fat-Sat orbital magnetic resonance imaging.
systemic corticosteroids. COVID-19 is known to induce an hyperimmune response with activation of T-cell and abnormal production of cytokine as it happens in other autoimmune conditions. It is also well known that viruses such as CMV and Epstein-Barr virus (EBV) can be a trigger for autoimmune pathologies. In fact, coronavirus infection has been associated with Kawasaki disease in children, Guillain-Barré syndrome and other autoimmune conditions in adults. There are also atypical cases reported in literature where a vaccine for shingles or H1N1 have been considered to be the trigger for orbital myositis. Some of them occurring hours after inoculation highlighting a hypersensitivity type reaction. Reports of myositis occurring after influenza vaccine have been even attributed to the immunogenicity of the adjuvant component of the vaccine and have been described as Shoendfeld’s syndrome or “autoimmune/inflammatory syndrome by adjuvants” (ASIA). The pathogenesis of the ASIA syndrome is founded on the hypothesis that the exposure to an adjuvant may set in motion a chain immunological events that, in susceptible individuals, may ultimately lead to the development of autoimmune disease. Our cases did not fulfill all the criteria to be identified as ASIA syndrome. The possibility that our patients developed a Graves” Disease following SARS-CoV-2 Vaccination can be excluded considering the serological thyroid hormones and autoantibodies within the normal ranges. Armstrong et al already highlight that the idiopathic orbital inflammation (IOI) is still poorly understood in terms of pathogenesis and the role of immunology is not clear. Myositis is a rare manifestation that in our first case we hypothesized has been triggered by COVID-19 vaccine in a patient likely to develop autoimmune reactions due to the ANCA-related vasculitis. This is the first time that OM and scleritis are related to COVID-19 mRNA vaccines, likely effect of an autoimmune reaction triggered by the virus antigen.

Ocular scleritis and orbital myositis can be idiopathic, or manifestations of many autoimmune conditions and the differential diagnosis can be challenging. No evidence of high circulating thyroid hormone levels, negative autoimmune serological tests and the onset in temporal relation (5–10 days) to the first or second dose of mRNA COVID vaccine should put on alert and suggest a vaccine (virus antigen) immunological reaction. It has to be noted that most of the patients had an underlying immune disorder that could contributed to the onset of the orbital myositis and sclerities. Pathophysiology of immune myositis is not yet understood. We can suppose that in certain individuals, with genetic predisposition, the mRNA vaccine may drive the activation of an immune response through activation of receptors expressed by orbital cells with increasing of proinflammatory cytokines and consequent inflammation, edema, and expansion of extraocular muscles. The immune system may therefore detect the mRNA in the vaccine as an antigen after the first dose then reacts to the antigen and activate the proinflammatory cascade and immunologic pathways after the second dose. The adverse effects following COVID-19 vaccine, as the ones that we reported, are generally reversible. Further studies in patients with undiagnosed autoimmune orbital and ocular diseases are needed, on larger samples, to confirm these results.

Consent

A statement of consent to publish these cases and the images were gathered from the patients.

Declaration of conflicting interests

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