Thieme

Biopsy-proven Orbital Sarcoidosis after SARS-CoV-2 mRNA Vaccination

Biopsiegesicherte orbitale Sarkoidose nach SARS-CoV-2-mRNA-Impfung

Introduction

Pfizer-BioNTech mRNA vaccine (BNT162b2) was used for immunization against Coronavirus disease 2019 (COVID-19). Many side effects involving different medical systems have been reported following widespread vaccination programs. The list of associated ocular inflammatory adverse events after administration of COVID-19 vaccines includes thyroid eye disease, orbital inflammatory pseudotumor, Tolosa-Hunt syndrome, superior ophthalmic vein thrombosis, choroiditis, nerve palsies, optic neuritis, corneal graft rejection, and uveitis [1–11]. To the best of the author's knowledge, no study has been found the orbital sarcoidosis following COVID-19 vaccination. We report a case of proven systemic sarcoidosis which also involved the orbit initially presenting as periorbital swelling after the second dose of the Pfizer-BioNTech mRNA vaccine. We believe this to be the first such report. This study adhered to the tenets of the Declaration of Helsinki.

Case Description

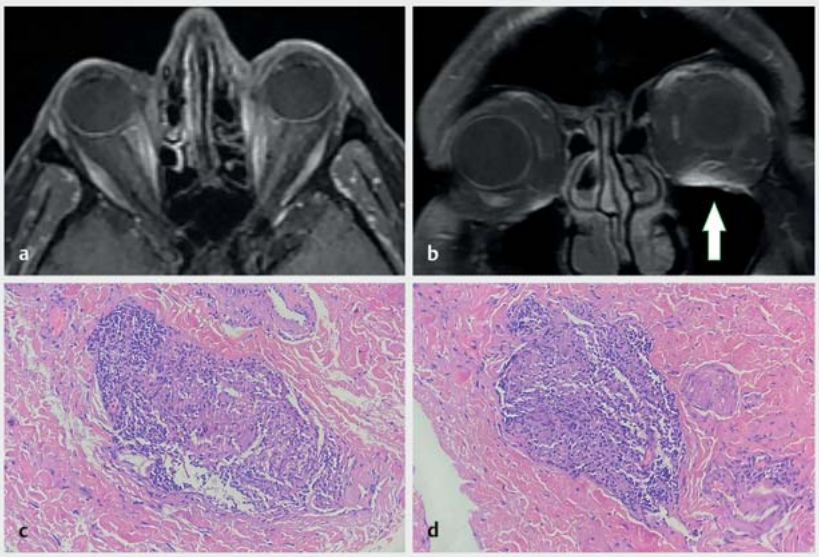
A 62-year-old man developed symptoms of swelling of the left periobital region in August 2021, one week after a second dose of the Pfizer-BioNTech mRNA vaccine (BNT162b2). He presented to another hospital in September 2021 where a preliminary diagnosis of orbital inflammatory pseudotumor was made. Systemic steroid treatment was administered. Only partial improvement was seen and the patient was referred to our hospital in October 2022.

His best-corrected visual acuity was 6/6 in each eye. Intraocular pressures were 17 and 18 mmHg in the right and left eyes, respectively. The pupils were equally round and reactive to light and accommodation, with no relative afferent pupillary defect. External examination was remarkable for periorbital edema and hyperemia of the left upper and lower eyelid (▶ **Fig. 1 a**). The swelling of the lower eyelid was firm on palpation with a diffuse, solid mass. The left eye demonstrated 1 mm of proptosis. The margin-to-reflex distance was 4 mm in the right and 2 mm in the left; levator function was 19 mm in both eyes. There was no restriction of eye movement and the patient denied any diplopia or pain on movement. Biomicroscopic and retinal examinations were normal.

Magnetic resonance imaging (MRI) of the orbit with contrast (▶ **Fig. 2 a**, **b**) revealed left T1 hyperintense, enhancing soft tissue extending from the left preseptal soft tissues into the extraconal fat with sparing of the optic nerve, cavernous sinus, and lacrimal gland. The patient was started with 40 mg prednisolone orally per day, but a partial response was observed despite six months of treatment (▶ **Fig. 1 b**). It was decided to proceed with orbital biopsy. The lower eyelid via subsilier incision was performed below the orbicularis oculi muscle. Orbital fat pads were observed rigid and dense intraoperatively. The histopathologic analysis showed non-necrotizing granulomatous inflammation consistent with sarcoidosis (▶ **Fig. 2 c**, **d**). Stains for acid-fast bacilli and fungi were negative. Additionally, systemic examination and laboratory tests were unremarkable, except for elevated ACE level (Supplemental Table, online). Quantiferon-gold, fluorescent treponemal antibody-absorption, rapid plasma reagin, and Epstein Barr virus PCR results were negative. The PET/CT scan performed to exclude malignancy revealed no findings suggestive of malignancy. CT chest without contrast was done due to the suspicion for sarcoidosis which showed hilar lymphadenopathy.

▶ **Fig. 1** **a** Initial image showing left periorbital edema and hyperemia (arrow). **b** Partial response after systemic corticosteroid treatment. **c** Good response following systemic methotrexate and corticosteroid therapy.

Klin Monatsbl Augenheilkd 2026; 243 |



▶ **Fig. 2** **a** Axial T1 MRI. **b** Coronal T1 MRI with GAD revealed left T1 hyperintense, enhancing soft tissue extending from the left preseptal soft tissues into the extraconal fat with sparing of the optic nerve, cavernous sinus, and lacrimal gland (arrow). **c, d** 20×, Hematoxylin and eosin-stained pathologic preparations of our patient's incisional biopsy revealing non-necrotizing granulomas and associated reactive lymphocytes in subcutaneous tissue. MRI, magnetic resonance imaging; GAD, gadolinium.

The patient was diagnosed with systemic sarcoidosis, and treatment was revised with methotrexate 15 mg orally per week and prednisolone 20 mg per day. Prednisolone was gradually tapered to a maintenance dose of 5 mg/day in 3 months. At follow-up approximately 5 months after methotrexate treatment initiation, the patient findings had largely resolved (▶ **Fig. 1 c**).

Discussion

The clinical, radiological and histopathological characteristics of a case with orbital sarcoidosis development following the COVID-19 vaccination are reported in the present study. The distinctive characteristic of this patient is the initial findings of periorbital edema and hyperemia of the left upper and lower eyelid. Despite the suspicion of sarcoidosis with an increased ACE level, inconclusive radiologic images, and partial response to systemic steroids necessitated a biopsy to confirm the diagnosis. The histologic evaluation demonstrated non-caseating granulomatous infiltration in the orbital fat, which was consistent with sarcoidosis, and infectious reasons were ruled out. Subsequent investigations demonstrated hilar lymphadenopathy on a chest imaging. The present case was diagnosed with systemic sarcoidosis.

To date, there are case series reporting ophthalmic side effects after COVID-19 vaccination such as uveitis, corneal graft rejection, optic neuritis, and peripheral ulcerative keratitis [5–8]. An orbital disorders related with COVID-19 vaccination remains far less common than other intraocular side effects. Any cases that triggered orbital inflammation, orbital myositis, dacryoadenitis, superior ophthalmic vein thrombosis, Tolosa-Hunt syndrome, and, thyroid eye disease after the COVID-19 vaccine have recently been reported [1–4, 9–11]. The common features of our cases with the previously reported cases were development following mRNA vaccines, the initiate of eye symptoms 1 day to 1 week following vaccination. While the published cases were treated with only systemic steroids, our patient had a partial response to systemic steroids. Our case was treated with systemic methotrexate and prednisolone.

Orbital sarcoidosis mostly exist as involvement of the lacrimal gland, however also can present as a diffuse, solid mass with irregular infiltration of orbital structures, extraocular muscles, or lacrimal sac [12, 13]. In the present case, diffuse, solid mass eyelid involvement demonstrating enhancement with contrast material on radiologic imaging. The most common signs of orbital sarcoidosis were those of inflammation: hyperemia and edema of the eyelids [12, 13]. Our patient also presented with these findings. Systemic corticosteroid treatment has been the standard treatment for orbital sarcoidosis [12, 13]. Prabhakaran et al. reported that 95% of their cases who were treated with systemic steroid treatment demonstrated complete or partial response [13]. One case (5%) failed to respond and required immunosuppressive treatment. In our case, the activation of the immune system by the two doses of mRNA vaccine administered may explain the partial response to steroid treatment.

The Pfizer-BioNTech mRNA vaccine is a lipid nanoparticle formulated with an mRNA encoding the SARS-CoV-2 spike (S) protein, which serves as both an immunogen and an adjuvant. It activates innate and adaptive responses against SARS-CoV-2 and exhibits 95% efficacy in preventing the disease [14]. Inflammation after COVID-19 vaccine suggests an immunological process targeting orbital tissue rather than direct viral infiltration, which has been hypothesized by some to be the underlying mechanism of COVID-19 infection associated eye disorders. The potential mechanism might have been an autoimmune inflammatory reaction to the viral antigens and/or vaccine adjuvants. In this case, the diagnosis of sarcoidosis is based on hilar adenopathy and biopsy, but there is no mention of the patient's health status prior to COVID vaccination. Sarcoidosis is a multi-system inflammatory disease. It may be possible that the patient had undiagnosed sarcoidosis which became evident around the same time as the vaccination.

To our knowledge, this is the first case of orbital sarcoidosis following COVID-19 vaccination. The presented case of orbital sarcoidosis following mRNA vaccine may be considered to be an immunological

process targeting the orbital tissue following immunization, although the cause-effect relationship remains uncertain. In summary, our report indicates a potential interest between orbital sarcoidosis and the mRNA vaccine. Further investigations are needed to elucidate the underlying immunological interactions and to establish a cause-effect relationship.

Informed Consent/ Patient Consent

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images. This case report is in compliance with the ethical principles outlined in the Declaration of Helsinki.

Conflict of Interest

The authors declare that they have no conflict of interest.

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