



Immunoglobulin (Ig) G4-related disease (IgG4-RD) is a systemic immune-mediated fibro-inflammatory disease characterized by elevated serum levels of IgG4, abundant infiltration of two or more organs with IgG4 positive plasma cells, and fibrosis of affected organs. It usually manifests with tumefactive lesions and fibrosis at multiple sites. The pathophysiology of IgG4-RD remains unknown, but, some previous data support autoimmunity as the underlying mechanism. In this case report, the Chinese authors present a patient who developed IgG4-RD with the ocular manifestation, referred to as IgG4-related ophthalmic disease (IgG4-ROD), after COVID-19 vaccination with inactivated vaccine.

In the IgG4-ROD, an ocular manifestation of IgG4-RD, the lacrimal gland is most commonly affected, but the orbital soft tissues, orbital nerves, sclera, choroid, and the orbital adnexa can also be affected. IgG4-ROD may be a bilateral disease.

There are currently no international standardized diagnostic criteria for IgG4-ROD. In 2015, the Japanese authors proposed the most recent diagnostic criteria: (1) the enlargement of the lacrimal gland, trigeminal nerve, or extraocular muscles, and the enlargement or hypertrophy of various ophthalmic tissues (2) a marked lymphocyte and IgG4-positive plasma cell infiltration and fibrosis, the ratio of IgG4- to CD38-positive cells (indicating the plasma cell ratio) of 40% or above, and (3) increased serum concentrations of IgG4  $\geq 135$  mg/dl. The diagnosis is categorized as “definitive” when all three criteria are fulfilled, “probable” when (1) and (2) criteria are fulfilled, and “possible” when (1) and (3) criteria are fulfilled.

The immune system dysfunction, caused by SARS-CoV-2 infection or COVID-19 vaccination, may be a key factor in the pathogenesis of IgG4-RD. Serum IgG4 levels were shown to predict the prognosis of COVID-19. Serum concentrations of IgG4  $> 700$  mg/dl and an IgG4/IgG1 ratio  $> 0.05$  were associated with an increased mortality at 30 days. In addition, a recent study that longitudinally monitored the IgG response has found that repeated mRNA COVID-19 vaccination increased the level of non-inflammatory IgG4 antibodies specific for the SARS-CoV-2 spike protein and IgG4-switched memory B cells for five to seven months after the second vaccination.

<https://discovermednews.com/repeated-sars-cov-2-mrna-vaccination-results-in-a-class-switch-to-noninflammatory-spike-specific-igg4-antibodies/> Furthermore, an increase in IgG4 levels specific for the SARS-CoV-2 spike subunit 1 (S1)-and receptor-binding domain (RBD) was observed in children one year after BNT162b2 vaccination.

<https://discovermednews.com/elevated-igg4-children-after-mrna-bnt162b2-vaccination/>



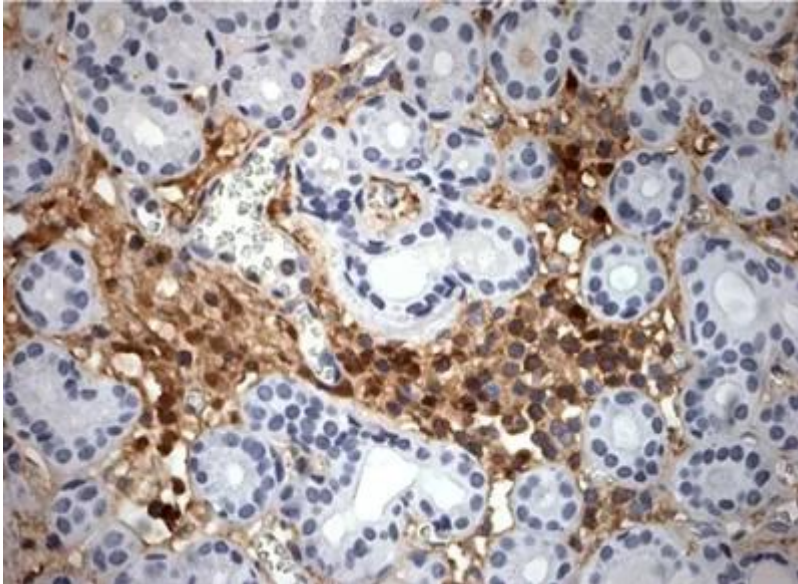
### ***About the case***

A 22-year-old healthy woman received an inactivated COVID-19 vaccine in May 2021 and had a fever for the following few days. After one month, she noticed a slight ptosis in the left eye and a mild loss of vision in the right eye. Orbital computed tomography (CT) revealed soft tissue swelling in the region of the left lacrimal gland. Funduscopy examination showed macular edema in the right eye. Fundus fluorescein angiography revealed tortuous fundus veins, anastomosed vessels in the optic disc and retina, and extensive dilatation of peripheral retinal vessels.

The patient was treated with anisodine, which was injected into the left superficial temporal artery, and with oral mecobalamin, Mongolian medicine, acupuncture, and electromagnetic therapy, but, her symptoms even worsened.

In August 2022, the patient was admitted to the ophthalmic ward. The visual acuity of the right eye was 0.3 and of the left eye 0.8. The ptosis of the left eye covered the pupil by more than half. A differential diagnosis of *myasthenia gravis* and Eaton-Lambert syndrome, which may cause ptosis, was ruled out by electromyography, the neostigmine test, and serum antibodies specific for neuromuscular diseases. Ocular ultrasound demonstrated an enlargement of the left lacrimal gland and a fullness of the right lacrimal gland. Magnetic resonance imaging showed an abnormal enhancement of the right optic nerve and its surrounding sheath.

Histopathological analysis of biopsy specimens from the left lacrimal gland, orbital septal tissue, and orbital fat revealed an inflammatory pseudotumor. Serum concentration of IgG4 was increased (280 mg/dl). All three diagnostic criteria were fulfilled for a definite diagnosis of IgG4-ROD.



The patient was treated with high-dose intravenous methylprednisolone pulse therapy and tacrolimus orally. She reported opening the eye more easily, but there was no significant change in the ptosis and vision loss. She continued to take methylprednisolone and tacrolimus orally after discharge.

In December 2022, the patient was infected with SARS-CoV-2, and the ptosis in her left eye and vision loss in her right eye worsened. She was readmitted to the hospital in August 2023. The visual acuity of the right eye was 0.15 and of the left 1.0. The ptosis of the left eye covered the entire pupil. The serum IgG4 was 240 mg/dl.

She underwent a surgical correction of ptosis of the left eye and bilateral eyelid plastic surgery. Histopathologic examination of the specimen from the muscle levator palpebrae superioris revealed fibrosis.

### *Conclusion*

According to the authors, this is the first reported case of IgG4-ROD after COVID-19 vaccination. The IgG4-related disease is a multiorgan disorder, but in the case presented in this study, only one organ was involved. The authors proposed two possible causes of the



patient's ptosis: the compression of the oculomotor nerve by the swelling of the orbital soft tissue, or the fibrosis of the levator muscle of the upper eyelid caused by IgG4-ROD. It was confirmed that central retinal vein occlusion caused the patient's vision loss in the right eye. Notably, a recent study has shown a 2.19 times higher overall risk of all forms of retinal vascular occlusion in the vaccinated individuals than in the unvaccinated cohort within the two years after the COVID-19 vaccination.

<https://discovermednews.com/retinal-vascular-occlusion-after-covid-19-vaccination/>

The authors mentioned that they have found nine previously published IgG4-RD cases that developed after the SARS-CoV-2 infection or vaccination. The four developed after the infection, and five after the vaccination. The interval between the onset of IgG4-RD symptoms and SARS-CoV-2 infection or vaccination varied from one day to three and a half months.

In this study, the onset of IgG4-ROD was closely related to SARS-CoV-2 infection and vaccination, but there was no direct evidence of a causal relationship. This association needs to be further investigated.

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### ***Journal Reference***

Zhang P, Wu Q, Xu X, Chen M. A case of IgG4-related ophthalmic disease after SARS-CoV-2 vaccination: case report and literature review. *Front. Immunol.*, 22 February 2024. Volume 15, 2024.

<https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2024.1303589/full>



IgG4-related ophthalmic disease after COVID-19  
vaccination (case report) | 5

