Immunoglobulin (Ig)G4-related disease (IgG4-RD) is a systemic immune-mediated fibro-inflammatory disease characterized by elevated serum levels of IgG4, an abundant infiltration of two or more affected 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 study, the Japanese authors presented two cases of IgG4-related diseases that developed after COVID-19 vaccination. In the first patient, IgG4-RD manifested with sialadenitis and pancreatitis, whereas the second patient developed IgG4-related hepatopathy.

COVID-19 is a clinical syndrome caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), an enveloped, positive-sense, single-stranded RNA virus. 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/

According to some authors, increased IgG4 levels detected after repeated vaccination with the mRNA vaccines are not a protective mechanism but rather an immune tolerance mechanism to the SARS-CoV-2 spike protein. Increased IgG4 synthesis due to repeated mRNA vaccination with high antigen concentrations could promote unopposed SARS-CoV2 infection and replication by suppressing natural antiviral responses, autoimmune diseases, and cancer growth in susceptible individuals. Uversky VN. et al. IgG4 Antibodies Induced by Repeated Vaccination May Generate Immune Tolerance to the SARS-CoV-2 Spike Protein. Vaccines 2023, 11, 991. https://doi.org/10.3390/vaccines11050991

The first study

The first study presented a case of a new-onset IgG4-related sialadenitis and pancreatitis that developed two weeks after receiving the mRNA BNT162b2 vaccine.

According to the authors, mRNA COVID-19 vaccination increased the number of adverse reaction reports, including new onset or exacerbation of various autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, autoimmune hepatitis, and thyroiditis. The main mechanisms believed to underlie the induction of autoimmunity by mRNA COVID-19 vaccines are molecular mimicry, specific vaccine adjuvant effects, and involvement of age-associated B cells.

The researchers emphasized that four cases of new-onset or relapsed IgG4-RD have already been reported after COVID-19 vaccination, making this case the fifth reported. Four individuals had received the BNT162b2 vaccine, whereas in one case the vaccine type was not specified. All cases received one or two doses of vaccines. The affected organs were the pancreas and liver, and the time between the onset/relapse of IgG4-RD and the COVID-19 vaccination varied from one to eight weeks.

About the case

A 78-year-old woman, with no history of autoimmune disease or COVID-19 infection, noticed bilateral swelling in her submandibular region two weeks after receiving a second dose of the BNT162b2 mRNA vaccine. Due to elevated serum levels of IgG4, the patient was referred to the hospital with a suspected diagnosis of IgG4-RD. A physical examination showed painless masses bilaterally in the submandibular region, with no other abnormalities. The laboratory analyses showed elevated concentrations of IgG (2,165 mg/dL, normal range 870-1,700 mg/dL), IgG4 (1,100 mg/dL, normal range 11-121 mg/dL), soluble interleukin-2 receptor (662.0 U/mL, normal range 157-474 U/mL), and C-reactive protein (0.49 mg/dL; normally less than 0.14 mg/dL). A whole-body computed tomography (CT) scan showed symmetrically enlarged submandibular glands and diffuse pancreatic enlargement with the loss of lobules. 18F-fluorodeoxyglucose-positron emission tomography demonstrated an abnormal accumulation in the submandibular glands and pancreas. The patient declined a biopsy of submandibular glands.

She was diagnosed with IgG4-RD according to the American College of Rheumatology/the European League Against Rheumatism classification criteria. Prednisolone treatment

resulted in a rapid shrinkage of the submandibular masses, while IgG4 levels gradually decreased. After four months, a CT scan demonstrated improvement in the submandibular gland and pancreatic enlargement.

This case showed the development of IgG4-RD, triggered by the mRNA COVID-19 vaccination, although the causal link between mRNA vaccines and the development of IgG4-RD was not confirmed.

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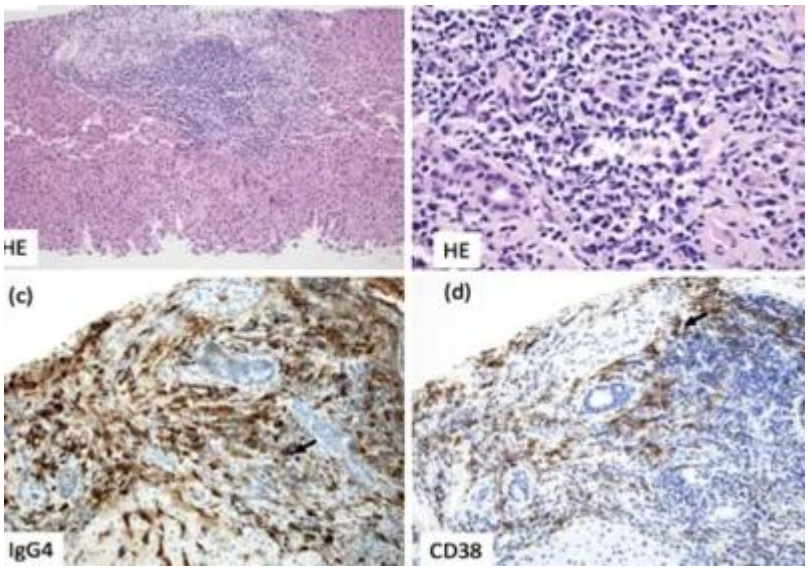
Journal Reference

Aochi S, Uehara M, and Yamamoto M. IgG4-related Disease Emerging after COVID-19 mRNA Vaccination. Intern Med 62: 1547-1551, 2023. (Open Access). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10258086/

The second study

Regarding liver involvement, IgG4-related disease can be manifested as IgG4-related sclerosing cholangitis, IgG4-related autoimmune hepatitis, and IgG4-related hepatopathy.



Liver biopsy findings. Original illustration from the study of Kuno M et al, 2023

This study presented a case of IgG4-related hepatopathy that developed after COVID-19 vaccination.

About the case

A woman aged 84 years experienced generalized itching, anorexia, and nausea one day after the first dose of the COVID-19 vaccine. When she was 80 years old, she was diagnosed with IgG4-RD, characterized by enlarged generalized lymph nodes, a mild enlargement of the submandibular glands, and elevated serum levels of IgG4. At that time, a lip biopsy revealed an IgG4:CD38-positive cell ratio (which indicates the plasma cell ratio) of more than 70%. At the age of 75, she underwent a left nephrectomy for kidney cancer.

Seven days after receiving the vaccine, she was hospitalized with bilateral swelling of the submandibular and axillary lymph nodes, and an enlarged liver, which was palpable two finger-breadths below the costal margin. Jaundice was seen all over her body.

The laboratory analyses showed elevated concentrations of aspartate aminotransferase at 113 U/L (normal range 3-38 U/mL), alanine aminotransferase at 110 U/L (normal range 4-44 U/mL), γ-glutamyl transpeptidase at 107 IU/L (normally less than 30 IU/L), IgG at 6,032 mg/dL (reference range 861-1,747 mg/dL), IgG4 at 2,934 mg/dL (normal ≥135 mg/dl), and IgE at 340 mg/dL (reference range 1,5-144 IU/mL). The results of immunological tests for various autoantibodies and hepatitis B and C were all negative.

The CT scans demonstrated an enlarged liver, spleen, and axillary, mediastinal, hilar, periaortic, and mesenteric lymph nodes. The magnetic resonance cholangiopancreatography showed no abnormalities in the bile duct system.

The patient had a liver biopsy. Histopathological examination of the specimens revealed enlarged portal areas, numerous lymphocytes and plasma cells, and a small number of eosinophils. There was no evidence of periportal hepatitis or lesions suggestive of IgG4-related sclerosing cholangitis. The bile ducts were free of inflammation. Immunostaining showed IgG4-positive cells that infiltrated the portal areas. The ratio of IgG4: CD38-positive cells (which indicates the plasma cell ratio) was elevated to 74%, consistent with IgG4-related hepatopathy.

As results failed to meet the diagnostic criteria for IgG4-related autoimmune hepatitis or IgG4-related sclerosing cholangitis, IgG4-related hepatopathy was diagnosed. According to

the authors, this is the first reported case of IgG4-related hepatopathy after COVID-19 vaccination, confirmed by liver biopsy. They pointed out that the study by Efe et al. reviewed 87 patients with liver injury following COVID-19 vaccination, but, IgG4-related hepatopathy was not reported.

Other studies also reported cases of IgG4-RD that developed after COVID-19 vaccination, like a case of IgG4-related pleural disease, confirmed by pleural biopsy, and a case of IgG4-related tubulointerstitial nephritis with renal function deterioration. Also, a recent study presented a case of IgG4-related ophthalmic disease that developed after the COVID-19 vaccination with the inactivated vaccine.
https://discovermednews.com/the-ocular-manifestation-of-igg4-related-disease-after-anti-sars-cov-2-vaccination/

It is worth noting that IgG4-related disease is a multiorgan disorder, but in the cases cited above, and in the present study, only one organ was involved.

This article was published in the Internal Medicine.

Journal Reference

Kuno M, Sawa N, Mizuno H, Oba Y, Ikuma D et al. Immunoglobulin G4-related Hepatopathy after COVID-19 Vaccination. Intern Med 2023; 62: 2139-2143. (Open Access).
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10400404/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