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Letter to the Editor

Increase in the number of new cases of ANCA-associated vasculitis in the COVID-19 vaccine era

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ABSTRACT

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is an autoimmune vasculitis characterized by the production of antibodies against ANCA, with unclear pathogenesis. With the ongoing COVID-19 pandemic, COVID-19 mRNA vaccination has been available in Japan since February 2021. Although autoimmune symptoms have been reported after COVID-19 vaccinations, there have been no clinical investigations regarding the relationship between COVID-19 mRNA vaccines and the pathogenesis of AAV. Thus, the present study aimed to investigate whether the administration of COVID-19 mRNA vaccines affects the development of AAV. The study identified patients with new-onset AAV who were MPO-ANCA or PR3-ANCA positive and met the entry criteria of the AAV EMA classification algorithm. The study compared the number of new AAV cases per year before and after the start of the COVID-19 mRNA vaccine program in Japan. The study found that the annual number of new cases of AAV in Japan's Nagasaki Prefecture increased by approximately 1.5-fold since the COVID-19 vaccine program was initiated, suggesting a possible link between the COVID-19 mRNA vaccines and the development of AAV. Although the study provides insight into the clinical evaluation and management of autoimmune symptoms following COVID-19 vaccination, further investigation of the possible association between COVID-19 mRNA vaccines and the pathogenesis of AAV is required.

Dear Editor,

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is an autoimmune vasculitis with a poor prognosis, characterized by necrotic lesions in small and medium-sized blood vessels. The pathogenesis of AAV, which is characterized by the production of antibodies to ANCA in the blood against a background of environmental and genetic factors, has not been established and remains the subject of various theories. The Coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused an unprecedented setback to the global economy and health. The worldwide COVID-19 vaccination program is one of the most effective interventions to significantly reduce severe illness and death due to SARS-CoV-2 infection, and COVID-19 mRNA vaccination has been available in Japan since February 17, 2021.

During the two-year period from February 2021 to February 2023, Japan successfully completed the COVID-19 vaccination program for the majority of its population, with >80% of eligible individuals completing two doses. However, many new autoimmune phenomena (e.g., immune thrombocytopenia, autoimmune liver disease, Guillain-Barre syndrome, IgA nephropathy, rheumatoid arthritis, and systemic lupus erythematosus) have been reported after COVID-19 vaccinations [1]. Whether the association between COVID-19 vaccine and autoimmune symptoms is coincidental or causal is still under debate.

Although there have been several case reports regarding COVID-19 mRNA vaccines and the pathogenesis of AAV [2–5], there have been no clinical investigations of the relationship between COVID-19 mRNA vaccines and the pathogenesis of AAV. To assess whether the administration of COVID-19 mRNA vaccines affects the development of AAV, we investigated the number of new AAV cases per year before and after the start of the COVID-19 mRNA vaccine program in Japan.

We identified patients with new-onset AAV examined at Nagasaki University Hospital who were MPO-ANCA- or PR3-ANCA-positive and met the entry criteria of the AAV EMA classification algorithm [6]. The Nagasaki University Institutional Review Board approved the study protocol (approval no. 23032016). We defined the 5-year period from February 17, 2016 to Feb. 16, 2021 as the "prior to vaccine initiation" period, and we defined the 2-year period from Feb. 17, 2021 to Feb. 16, 2023 as the period "after vaccine initiation." The date of AAV onset was defined as the date of the first appearance of symptoms that the attending physician considered symptoms associated with AAV.

The number of new AAV patients was 46 cases/5 years (average: 9.2 cases/year) during the period prior to vaccine initiation. A considerable increase in the number of new AAV patients was observed after the initiation of the vaccine program: 32 cases/2 years (average: 16 cases/year) (Fig. 1).

It has been reported that COVID-19 infection causes vascular endothelial cell and microvascular damage, and that thrombotic microangiopathy contributes to the severity of the disease [7]. The similarity in pathogenesis between AAV and COVID-19, which is primarily associated with microvascular inflammation, has attracted attention.

Our observations indicate that the annual number of new cases of AAV in Japan's Nagasaki Prefecture has increased by approx. 1.5-fold since the COVID-19 vaccine program was initiated. Our data suggest that there could be a possible link between the COVID-19 mRNA vaccines and the development of AAV. In the present investigation, only the number of new AAV cases was analyzed, without information about the patients' vaccinations. The presence of confounding factors such as the development of COVID-19 itself was not controlled. Further investigation of the possible association between COVID-19 mRNA vaccines and

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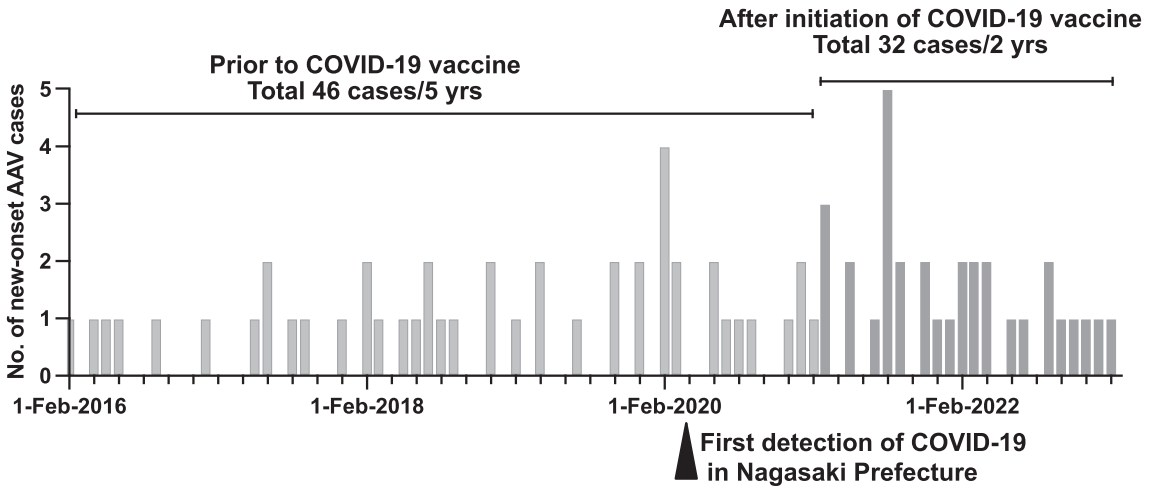

Fig. 1. Number of new cases of ANCA-associated vasculitis at Nagasaki University Hospital before and after the initiation of the COVID-19 vaccine program in Japan.

the pathogenesis of AAV would require a precise epidemiological design such as a self-controlled case series study with a large amount of data.

In sum, although sufficient evidence that the COVID-19 vaccines reduce the risk of severe illness and death caused by COVID-19 itself has been accumulated, it remains necessary to evaluate vaccine side effects. The data described above may provide insight into the clinical evaluation and management of autoimmune symptoms following COVID-19 vaccination.

Declaration of Competing Statement

The authors have no conflicts of interest or other disclosures to describe.

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Author contributions

ST, MU, and TK conceived and designed the study. ST, MU, SS, TS, TK, YF, and AK performed the data analysis and interpretation. ST and MU drafted the manuscript.

Key message

An increase in new ANCA-associated vasculitis cases occurred after the COVID-19 vaccine rollout.

Data availability

The data that has been used is confidential.

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