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Amyloid β-related angiitis of the central nervous system occurring after COVID-19 vaccination: A case report

Amyloid β-related angiitis after COVID-19 vaccination

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Abstract

BACKGROUND

Although the coronavirus disease-2019 (COVID-19) vaccine has been effective in suppressing the COVID-19 pandemic, a variety of post-vaccination neurological complications have been reported worldwide. Amyloid β-related angiitis (ABRA) is a rare neurological disease. The underlying cause of ABRA is unknown, but several studies suggest that it is caused by an excessive immune response to amyloid-β deposited in blood vessels. In addition, there has been little focus on potential triggers of ABRA, such as infection or vaccination.

CASE SUMMARY

We report a case of amyloid β-related angiitis (ABRA that developed 2 wk after COVID-19 vaccination. A 75-year-old woman developed a frontal headache after receiving her second dose of the COVID-19 vaccine (Pfizer-BioNTech). Diffusion-weighted magnetic resonance imaging (DW-MRI) of the head showed abnormal hyperintensity, suggesting cerebral infarctions in the left parietal and occipital lobes. We diagnosed her condition as ABRA based on a brain biopsy. We administered steroidal pulse therapy and the patient's symptoms and DW-MRI abnormalities improved. This case had a good outcome due to prompt diagnosis and treatment.

CONCLUSION

We report a case of ABRA that may have been triggered by COVID-19 vaccination.

Key Words: Amyloid β-related angiitis; Case report; COVID-19; Neurological complications; Vaccination

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Core Tip: Amyloid β-related angiitis (ABRA) is a rare neurological disease with overlapping features of cerebral amyloid angiopathy and primary angiitis of the central nervous system. We present a case of ABRA that appeared 2 wk after COVID-19 vaccination. The patient was diagnosed with ABRA based on brain biopsy. Steroidal pulse therapy was performed, and, the patient's symptoms and diffusion-weighted magnetic resonance imaging abnormalities improved. This case had a good outcome due to prompt diagnosis and treatment. Although the relationship between ABRA and COVID-19 vaccination are unclear, this case contributes to the literature on adverse neurological events following COVID-19 vaccination.

INTRODUCTION

Severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus that gave rise to the coronavirus disease 2019 (COVID-19) pandemic[1,2]. COVID-19 vaccines have been effective in suppressing the pandemic; however, a wide variety of neurological complications have been reported worldwide following COVID-19 vaccination[1,2].

Several types of vaccines are associated with a risk of a variety of serious neurological complications[1-3]. Neurological complications after vaccination can be explained by several pathogenic mechanisms, including molecular mimicry, direct neurotoxicity, and abnormal immune response[1].

Amyloid β-related angiitis (ABRA), also known as amyloid β-related vasculitis, is a rare neurological disorder. Although the causes of ABRA have not been clearly elucidated[4-7], several studies have suggested that ABRA is caused by an excessive immune response to amyloid-β deposited in the blood vessels[4,8,9].

However, there has been little focus on the triggers of ABRA, such as infection or vaccination. Currently, there is no evidence showing that COVID-19 vaccine triggers ABRA. Herein, we report a case of ABRA that developed 2 wk after COVID-19 vaccination. Although the causal relationship between the COVID-19 vaccine and

ABRA is unclear, we report this case to contribute to the existing literature in order to enable a better understanding of the etiology and triggers of ABRA.

CASE PRESENTATION

Chief complaints

A 75-year-old Japanese woman weighing 47 kg received the BNT162b2 COVID-19 vaccine (Pfizer-BioNTech) in late June 2021, and she did not experience any adverse effects. Three weeks later, in early July, she received the second dose of the vaccine. She developed a frontal headache after receiving the second vaccination. This post-vaccination headache improved within a few days.

History of present illness

Two weeks after the second vaccination, the patient's headache worsened, and she subsequently developed progressive depression, aphasia, apraxia, and gait disturbance. She was admitted to the hospital for further investigation and treatment.

History of past illness

The patient's medical history included hypertension, hyperlipidemia, and osteoarthritis. Her drug history included a regular use of 5 mg of amlodipine per day for the treatment of hypertension. Additionally, the patient took one tablet of paracetamol (200 mg) when she had back pain.

Personal and family history

The patient's brother had a history of cerebral infarction. There was no known family history of vasculitis or autoimmune disease.

Physical examination

On admission, the patient had a temperature of 36.7°C, a heart rate of 67 bpm, a blood pressure of 167/91 mmHg, and an oxygen saturation of 98% at room air. A neurological

examination showed that the patient had right upper limb weakness and hyperreflexia in both arms, both of which are pyramidal signs, and confirmed that she had aphasia and apraxia.

Laboratory examinations

Laboratory findings showed no abnormalities in the complete blood count, biochemistry, or coagulation tests. The complete blood count results were: white blood cell count, $5.15\times10^3/\mu L$ (reference: $3.3–8.6\times10^3/\mu L$); red blood cell count, $4.52\times10^6/\mu L$ (reference: $3.8–5.0\times10^6/\mu L$); and platelet count of $150\times10^3/\mu L$ (reference: $150–350\times10^3/\mu L$). The differential leukocyte count results were: neutrophils, $3.31\times10^3/\mu L$ (reference: $1.20\text{-}6.60\times10^3/\mu L$); lymphocytes, $1.09\times10^3/\mu L$ (reference: $0.50\text{-}4.30\times10^3/\mu L$); eosinophils $0.34\times10^3/\mu L$ (reference: $\leq0.80\times10^3/\mu L$), and basophils $0.03\times10^3/\mu L$ (reference: $\leq0.03\times10^3/\mu L$). The leukocyte percentages were 64.2% neutrophils (reference: 38.5–76.5%), 21.1% lymphocytes (reference: 16.5–49.5%), 5.7% monocytes (reference: 2.0–10.0%), 6.6% eosinophils (reference: ≤8.5%), 0.6% basophils (reference: ≤2.5%) and 1.7% large non-pigmented cells (reference: ≤4.0%). The hematology results were relatively normal, with mild eosinophilia at the onset, but the changes were within normal limits. The immune response appeared to be localized rather than systemic.

Blood biochemistry showed a C-reactive protein level of 0.04 mg/dL (reference: ≤0.14 mg/dL). Autoantibody test results for antinuclear antibody, antiribonucleoprotein antibody, anti-Smith antibody, anti-Ro (SSA) and anti-La (SSB) antibodies, cytoplasmic-antineutrophil cytoplasmic antibody (C-ANCA), and perinuclear-antineutrophil cytoplasmic antibody (P-ANCA) were negative. The reference values for the autoantibody tests were as follows: anti-Smith antibody-EIA, ≤10.0 U/mL; anti-SSA antibody-EI, ≤10.0 U/mL; anti-SSB antibody-EI ≤10.0 U/mL; C-ANCA) ≤3.5 IU/mL; P-ANCA ≤3.5 IU/mL. Cerebrospinal fluid tests were not performed because the patient's neurological symptoms and imaging findings suggested increased intracranial pressure.

Imaging examinations

Magnetic resonance imaging showed abnormal hyperintensity, suggesting cerebral infarctions in the left parietal and occipital lobes. These lesions were not consistent with the vascular territory (Figure 1).

FINAL DIAGNOSIS

Brain biopsy of the left occipital lobe revealed granulomatosis vasculitis with multinucleated giant cells in the leptomeningeal small vessels and fibrinoid necrosis of the vessel wall (Figure 2A). In addition, microhemorrhages were found in the subarachnoid space (Figure 2A). Immunohistochemical staining against amyloid-β revealed its deposits in the blood vessel wall (Figure 2B) and multinucleated macrophages phagocytosing amyloid-β (Figure 2C), consistent with a diagnosis of amyloid β-related vasculitis.

This finding corresponds to probable cerebral amyloid angiopathy (CAA) with supporting pathology according to the modified Boston criteria for CAA[10]. However the strong reaction of lymphocytes and histiocytes to amyloid-β in the vascular wall led to the diagnosis of ABRA.

TREATMENT

The patient was treated with steroid pulse therapy. The diagnosis was made immediately after brain biopsy, and steroid pulse therapy was initiated on the same day. Prednisolone (1000 mg/day) was administered intravenously for 3 days followed by prednisolone (80 mg/day) intravenously on the 4th day. On day 5, the steroid was switched to oral prednisone (45 mg/day) for 2 wk, and then tapered by 5 mg each week until the dose was 20 mg/day. The patient was maintained on a dose of prednisolone of 20 mg/day. The steroid pulse therapy was effective in relieving the headache, gait disturbance, and weakness in her arms, and the MRI abnormalities improved, but her aphasia and apraxia persisted.

OUTCOME AND FOLLOW-UP

The patient was discharged 90 days after the onset of her headache. Since her discharge 3 mo ago, she has had monthly follow-up visits to our hospital, and her condition has remained stable. Regarding future vaccinations, the patient's preferences will be considered, and a careful decision will be made based on the risks and benefits.

DISCUSSION

Several types of vaccines are associated with a risk of a variety of serious neurological complications[1-3]. Neurological complications after vaccination can be explained by several pathogenic mechanisms, including molecular mimicry, direct neurotoxicity, and an abnormal immune response[1,2].

ABRA is a rare neurological disease that is classified as a primary angiitis of the central nervous system (PACNS). It shares characteristics of both PACNS and cerebral amyloid vasculopathy (CAA)[4-7,11]. CAA is characterized by deposition of amyloid-β in the cortical and leptomeningeal vessels[4-7,11]. Vascular inflammation can also be present in amyloid-affected vessels; two types of inflammatory responses have been reported: ABRA and CAA-associated inflammation (CAA-RI). CAA-RI is characterized by an inflammatory response surrounding amyloid-laden vessels without vasodestructive features[4-7,11]. ABRA is a granulomatous, vasodestructive vasculitis characterized by abundant amyloid-β deposition in the vessel wall, affecting the subarachnoid and cortical blood vessels[4-7,11]. Although ABRA has the features of CAA with age-related changes, we do not believe that it can be attributed to age due to the excessive immune response to amyloid-β.

The causes of ABRA are currently unknown; however, several studies suggest an abnormal immune response to amyloid-β as the primary cause of ABRA[8,9,11,12]. The theory hypothesizes that ABRA is an immunological response to amyloid-β, which has been implicated in subarachnoid and cortical vasculitis with amyloid-β deposition and increased clearance[4,12]. In other words, ABRA is caused by inflammation that occurs as a result of an excessive immune response to amyloid-β deposition in the blood vessels[8,9,12]. The pathology of this case showed that the angiopathy met the Boston

criteria for CAA and indicated age-related changes, but the destructive vasculitis and phagocytosis of amyloid-β by macrophages indicated that the inflammatory changes to amyloid-β could not be attributed solely to age [10].

Currently, limited research has been conducted on triggers for ABRA, such as infection or vaccination. The lack of knowledge about factors that may trigger ABRA made this case extremely difficult to understand.

Furthermore, to the best of our knowledge, there have been no previous reports of ABRA following vaccination, making it difficult to infer a causal relationship between the vaccination and ABRA in the present case. Moreover, there are no reports of similar closely related diseases such as CAA and CAA-RI post vaccination. Additionally, ABRA has not been reported in association with SARS-CoV-2 infection. Nevertheless, an excessive immune response may occur following vaccination, which could explain the association between ABRA and vaccination for COVID-19.

In this case, there were no factors present other than the vaccine, that could have triggered an immune disorder, so the diagnosis of ABRA is consistent with an abnormal response to a COVID-19 vaccine. However, identifying the cause or triggers of ABRA requires a detailed analysis of the immune mechanism at the molecular level, which is difficult to perform in a community hospital. Therefore, we were unable to identify the trigger factors in this case. This patient was diagnosed and treated promptly resulting in a relatively good outcome. Thus, it is imperative to share knowledge of suspected adverse reactions to COVID-19 vaccines as this could aid in timely diagnosis and treatment of patients with similar symptoms in the future.

CONCLUSION

In our case of ABRA, there were no pre-existing factors other than the vaccine that may have led to an abnormal immune response; therefore, we suspect that ABRA was triggered by the second vaccination for COVID-19.

Long-term observations of adverse reactions are warranted to confirm a causal relationship between adverse neurological events and COVID-19 vaccination, which

could further aid in timely diagnosis and treatment of patients with similar symptoms in future.

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