Cervical Transverse Myelitis Following COVID-19 Vaccination

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Abstract

Various COVID-19 vaccines are associated with numerous adverse side effects. Associations between vaccinations and neurological disorders, such as transverse myelitis, stroke, Bell’s palsy, acute disseminated encephalomyelitis, and Guillain-Barré syndrome, have been reported. A 27-year-old Japanese woman presented with paresthesia four days after receiving a second dose of the COVID-19 vaccine. One month after vaccination, she started to feel left lower limb weakness, and her symptoms almost improved after two steroid pulse therapies. Spinal cord tumor biopsy could potentially help make a definitive diagnosis in clinical situations. However, it is very important to review the patient’s medical history, including vaccinations received, before performing a direct spinal cord biopsy, which is invasive and does not guarantee a definitive diagnosis.

Keywords: COVID-19, methylprednisolone, transverse myelitis, vaccination

Introduction

Many vaccines for COVID-19 have been administered worldwide; however, there are many adverse effects observed. A previous investigation of the major neurological complications of COVID-19 vaccination identified tremors, diplopia, tinnitus, dysphonia, seizures, facial palsy, the reactivation of herpes zoster, transverse myelitis (TM), stroke, Bell’s palsy, acute disseminated encephalomyelitis, and Guillain-Barré syndrome as possible side effects.1 Herein, we report a Japanese woman’s case of TM following a second dose of COVID-19 vaccination with some literature review.

Case Report

Four days after receiving the second dose of the BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine, a 27-year-old Japanese woman presented with right lower limb paresthesia. Except for mild malaise for a few days after vaccination, she reported no other side effects after each dose. Paresthesia gradually developed in the left hand and right lower body. One month after vaccination, she started to feel left lower limb weakness. Eventually, she could not lift her leg when going up the stairs. One and a half months after onset, she was referred to our hospital outpatient department for further investigation. Gadolinium-enhanced magnetic resonance imaging (MRI) revealed spinal cord swelling mainly at left-sided C5-7 levels with peripheral enhancement, suggestive of inflammatory or demyelinating diseases (Fig. 1A-C). Two days later, she began to have urinary incontinence and rectal disturbance. Moreover, her left paresthesia gradually ascended to the left chest and upper limb. Two months after vaccination, she was brought to our hospital by ambulance due to worsening symptoms and admitted.

She had no remarkable past medical history, except for a rectovaginal fistula during childbirth. She breastfed her baby the day before emergent admission. Neurological examination revealed mainly Brown-Séquard syndrome. On the manual muscle test, her bilateral lower limbs and left upper distal muscle strengths decreased to 4 points out of 5. The sensation was also reduced in the right trunk (below the C5 dermatomal level), right lower, and left upper limbs. She did not show hyperreflexia in either limb. Bladder and bowel dysfunction (BBD) gradually progressed.

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Routine serum examinations, including tumor markers, were negative. Regarding autoantibodies, only an anti-SSA antibody was elevated to 240 U/mL (base value, <7 U/mL). The soluble interleukin-2 receptor level was 301 U/mL (normal range: 145-519 U/mL). Serum cell-based anti-aquaporin-4 (AQP-4) and anti-myelin oligodendrocyte (MOG) antibodies were negative. Initial cerebrospinal fluid (CSF) examination revealed a mildly elevated protein level of 43 (base value, <40) mg/dL and a marked increase in myelin basic protein to 1,693.3 (base value, <102) pg/mL. The CSF bacteriological culture test result was negative without abnormal cells. Serum T-SPOT test (Oxford Immunotec Global PLC, Oxfordshire, UK) and antibody for human T-lymphotropic virus type 1 were negative. SARS-COV-2 RNA polymerase chain reaction nasal swab was negative on admission. Brain MRI did not reveal any abnormality. Table 1 summarizes the examination results.

Based on these comprehensive investigations, we suspected TM. On the fourth day after admission, she was administered the first pulse therapy with 1,000 mg of intravenous methylprednisolone (IVMP) for three days as diagnostic treatment. After pulse therapy, paresthesia and BBD improved slightly. Gadolinium-enhanced MRI after the first IVMP revealed regression of the spinal cord swelling and diminished enhanced lesions. She received a second pulse therapy with the same regimen two weeks after admission.
Table 1  Summary of examination results

| Parameter                        | Results     | Reference value |
|----------------------------------|-------------|-----------------|
| White blood cell count           | 6,100       | 3,300-8,600/μL  |
| Red blood cell count             | 526         | 386-492 ×10^6/μL|
| Hemoglobin                       | 12.4        | 11.6-14.8 g/dL  |
| Platelet                         | 32.5        | 15.8-34.8 ×10^4/μL|
| Hematocrit                       | 39.4        | 35.1-44.4%      |
| CRP                              | 0.02        | <0.30 mg/dL     |
| LDH                              | 14          | 0-25 U/L        |
| ACE                              | 13.5        | 7.7-29.4 IU/L   |
| TSH                              | 1.54        | 0.50-5.00 μIU/mL|
| Free T3                          | 2.53        | 2.30-4.30 pg/mL |
| Free T4                          | 1.44        | 0.90-1.70 ng/dL |
| sIL-2R                           | 301         | 145-519 U/mL    |
| PT-INR                           | 0.94        | 0.8-1.2%        |
| APTT                             | 30.4        | 24-40 sec       |
| D-dimer                          | 0.3         | <1 μg/mL        |
| β-D Glucan                       | 14.4        | <20 pg/mL       |
| Anti-SS-A antibody               | >240        | <7.0 U/mL       |
| Anti-SS-B antibody               | 0.5         | <7.0 U/mL       |
| ANA                              | 40          | <40             |
| PR3-ANCA                         | <0.6        | <2.0 IU/mL      |
| MPO-ANCA                         | <0.2        | <3.5 IU/mL      |
| Anti-Aquaporin 4 antibody        | negative    | negative        |
| Anti-MOG antibody                | negative    | negative        |
| IgG                              | 1434        | 870-1700 mg/dL  |
| IgA                              | 302         | 110-410 mg/dL   |
| IgM                              | 190         | 46-260 mg/dL    |
| C3                               | 89          | 86-160 mg/dL    |
| C4                               | 16          | 17-45 mg/dL     |
| HTLV-1                           | negative    | negative        |
| T-spot                           | negative    | negative        |
| CSF cell number                  | 7           | <5/μL           |
| CSF glucose                      | 59          | 50-75 mg/dL     |
| CSF protein                      | 43          | 10-40 mg/dL     |
| CSF MBP                          | 1,693.30    | <102 pg/mL      |
| IgG Oligoclonal band             | negative    | negative        |

CRP: C-reactive protein, LDH: lactate dehydrogenase, ACE: angiotensin converting enzyme, TSH: thyroid stimulating hormone, T3: triiodothyronine, T4: thyroxine, sIL-2R: soluble interleukin-2 receptor, ANA: antinuclear antibody, PR3-ANCA: serine proteinase3 anti-neutrophil cytoplasmic auto-antibodies, MPO-ANCA: myeloperoxidase anti-neutrophil cytoplasmic autoantibodies, MOG: myelin-oligodendrocyte glycoprotein, Ig: immunoglobulin, C3: complement 3, C4: complement 4, HTLV-1: Human T-cell leukemia virus type 1, CSF: cerebrospinal fluid, MBP: myelin basic protein

Subsequent MRI with contrast after the second IVMP revealed regression of the spinal cord swelling and less enhanced lesions (Fig. 1D-F). After two treatments, her motor weakness and BBD recovered, but paresthesia of the trunk and limbs partially remained. She continued treatment as an outpatient without medications.

**Discussion**

PubMed reported 14 previous cases of COVID-19 vaccination-induced TM worldwide (Table 2). These 15 cases, including our presented case, have a median patient age of 51.5±18.9 (27-78) years, and the male: female ratio was 8:6. Half of the patients received AstraZeneca vaccines, while the remaining received other vaccines. Of the 15 cases, nine developed myelopathy after the first dose and two after the second. There was no information about the first or second vaccination in four cases. The period from vaccination to symptom onset was 8.2±5.8 days (1-21 days). Offending lesion levels were almost identical at the cervical and thoracic levels. However, idiopathic TM most commonly occurs in the thoracic cord, with about 10% in the cervical cord. For the primary treatment, IVMP was administered in most cases. If there were inadequate responses, plasmapheresis or oral prednisolone was used as the following treatments. Ultimately, the symptoms recovered in almost all cases. Thus far, the short-term outcomes of COVID-19 vaccination-induced TM were relatively good; however, further studies on the possibility of relapse are needed.

Transverse myelitis is a rare phenomenon with an estimated incidence of between 1.34 and 4.6 cases per million annually. Several TM cases reportedly occurred following administration of different vaccines, such as hepatitis B virus, human papillomavirus, seasonal influenza, measles-mumps-rubella, polio, and diphtheria, that occurred from a few days to 3 months after vaccination. Currently, over ten cases of TM-associated COVID-19 vaccination have been reported. An exclusion diagnosis usually diagnoses TM, and its differential diagnoses include neuromyelitis optica spectrum disorder (NMOSD), multiple sclerosis (MS), and infectious causes. Negative oligoclonal bands and the absence of both AQP-4 and MOG antibodies make the diagnosis of NMOSD and MS unlikely, respectively. Molecular mimicry, epitope spreading, or polyclonal activation of B lymphocytes are possible mechanisms. Bhat et al. reported an association between TM and autoimmune diseases. Our patient had no history of autoimmune diseases, but an anti-SSA antibody associated with Sjögren’s syndrome was elevated. This may suggest the possibility of autoimmune diseases, but there was no definite proof.

In the presented case, neuroimaging was inconsistent with an intramedullary tumor because of circumferential enhancement, and her clinical course was too rash as spinal tumors. We suspected inflammatory diseases of unknown origin; therefore, diagnostic treatment was performed with steroid pulse therapy, which led to a favorable outcome.
Table 2 Summary of the published cases of COVID-19 vaccination-induced transverse myelitis

| No. | Reference | Age | Sex | Comorbidities | Brand of vaccine | First or second vaccination | Onset time | Involved regions | Managements | Outcome |
|-----|-----------|-----|-----|---------------|------------------|----------------------------|------------|-----------------|-------------|---------|
| 1   | Gao et al., 2021 ¹ | 76  | M   | None          | Moderna          | N/A                       | 6 days     | C2-5, T1       | IVMP, oral-PSL, hydroxocobalamin | Improvement |
| 2   | Khan et al., 2021 ² | 67  | F   | Heart and Kidney disease, Neuropathy, Colon rupture | Moderna          | 1st | 1 day | C1-3 | IVMP | Improvement |
| 3   | Notghi et al., 2021 ³ | 58  | M   | DM           | AstraZeneca      | 1st | 7 days | T2-10 | IVMP, oral-PSL, PP | Improvement |
| 4   | Malhotra et al., 2021 ⁴ | 36  | M   | None          | AstraZeneca      | 1st | 8 days | C6-7 | IVMP | Improvement |
| 5   | Pagenkopf et al., 2021 ⁵ | 45  | M   | Atopic dermatitis | AstraZeneca   | 1st | 8 days | C3-T2 | IVPSL | Improvement |
| 6   | Hsiao et al., 2021 ⁶ | 41  | M   | DM           | AstraZeneca      | 1st | 2 weeks | T1-6 | IVMP, oral-PSL | Improvement |
| 7   | Vegezzi et al., 2021 ⁷ | 44  | F   | None          | AstraZeneca      | 1st | 4 days | T7-8, T10-11 | IVMP | Improvement |
| 8   | Han et al., 2021 ⁸ | 25  | F   | N/A          | AstraZeneca      | 1st | 16 days | T3-5, T7-8, T11-L1 | IVMP | Improvement |
| 9   | Erdem et al., 2021 ⁹ | 78  | F   | N/A          | CoronaVac        | N/A | 3 weeks | C1-T3 | N/A | N/A |
| 10  | Tahir et al., 2021 ¹⁰ | 44  | F   | None          | Johnson & Johnson | N/A | 10 days | C2-3, T2 | IV-PSL, PP | Improvement |
| 11  | Miyake et al., 2021 ¹¹ | 75  | M   | HT, HL, Prostate cancer | Pfizer          | 1st | 3 days | T11-L1 | IVMP, oral-PSL, PP | Partial improvement |
| 12  | Cabral et al., 2022 ¹² | 33  | M   | None          | Pfizer          | 2nd | 2 days | Unremarkable | None | Improvement |
| 13  | Sepahvand et al., 2022 ¹³ | 71  | M   | DM, HT, Heart disease | Sinopharm        | 1st | 5 days | Medullary-C3 | IVMP | Improvement |
| 14  | Roman et al., 2021 ¹⁴ | N/A | N/A | None          | AstraZeneca      | N/A | 14 days | N/A | N/A | N/A |
| 15  | Our presented case | 27  | F   | Breast-feeding | Pfizer          | 2nd | 4 days | C5-7 | IVMP | Improvement |

[Abbreviations] DM: diabetes mellitus, F: female, HT: hypertension, HL: hyperlipidemia, IVMP: intravenous methylprednisolone, M: male, N/A: not assigned, PP: plasmapheresis, PSL: prednisolone

outcome. The sensitivity of spinal cord MRI is high, but the diagnostic specificity is not sufficient. Direct spinal cord biopsy is invasive and challenging only for diagnosis in such a case. When the lesion is not a neoplasm, the cause of the disease may not be diagnosed, even after biopsy. Therefore, it is very important to check the patient's medical history, including vaccination status, when the MRI shows atypical images of the lesion.

Conclusion

This case illustrated a temporal link between the COVID-19 vaccine and neurological conditions, which should be considered after excluding other possible diseases through comprehensive investigations. When the cause of a lesion cannot be determined, a direct spinal cord biopsy could help confirm a definitive diagnosis. However, it is imperative to check the patient's medical history, including vaccinations received, prior to performing a direct spinal cord biopsy, which is invasive and does not guarantee a definitive diagnosis.

Informed Consent

The consent from all participants was obtained.

Conflicts of Interest Disclosure

The authors have nothing to disclose.

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