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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 BNT162 b2 (Pfizer-BioNTach) 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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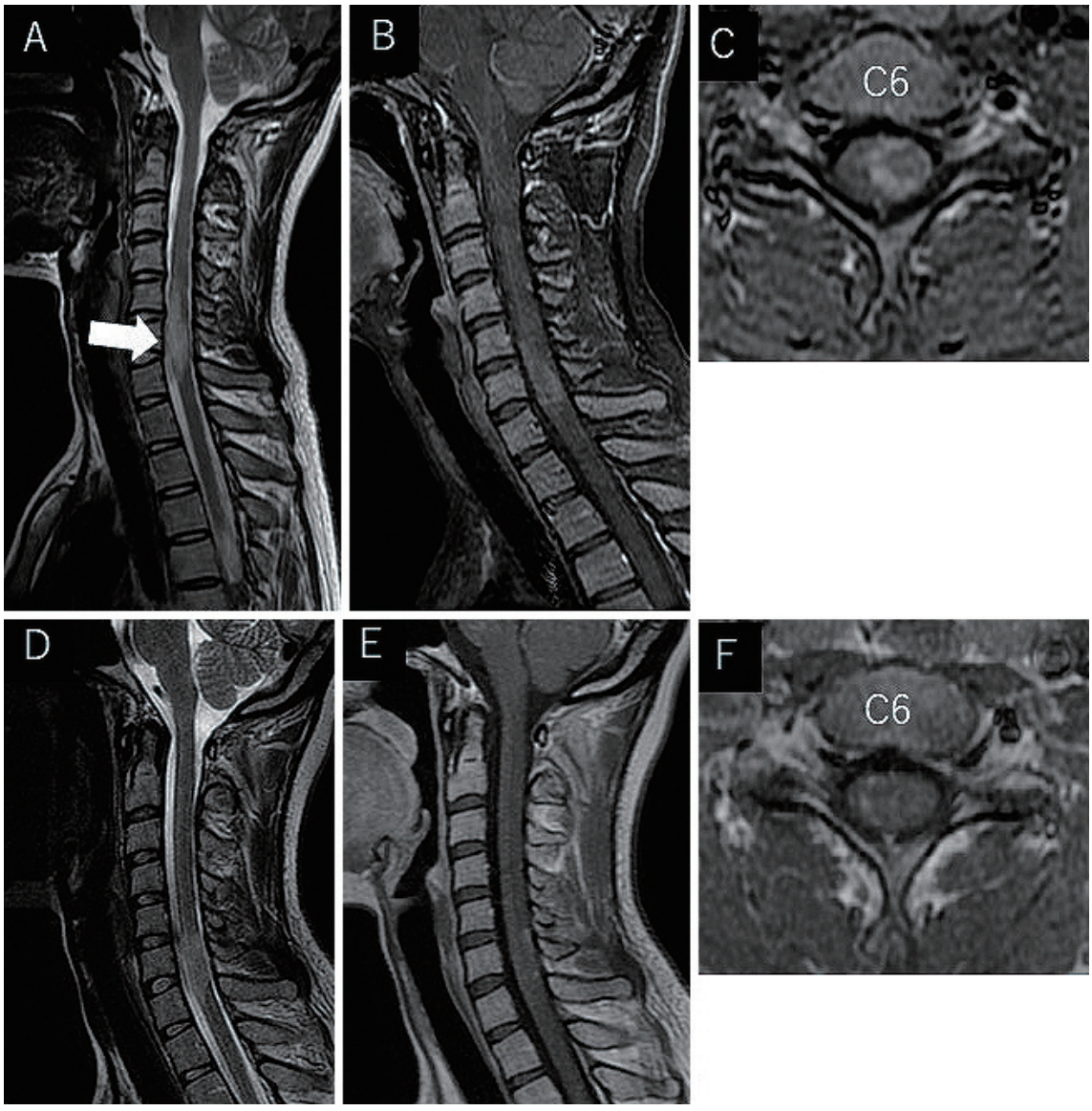

Fig. 1 Initial magnetic resonance imaging (MRI) with contrast on admission. (A) T2-weighted and (B, C) post-contrasted T1-weighted images showed spinal cord swelling with peripheral enhancement mainly located at the left-sided C5-7 levels (white arrow). Subsequent MRI with contrast medium after secondary intravenous methylprednisolone demonstrated regression of the spinal cord swelling and diminished enhanced lesions (D: T2-weighted, E, F: post-contrasted T1-weighted images).

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 $\times 10^4$/μL
Hemoglobin	12.4	11.6-14.8 g/dL
Platelet	32.5	15.8-34.8 $\times 10^4$/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 autoantibodies, 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).[1-14] 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 (one case was not assigned). 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.[15] 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.[8] 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.[12] 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.[8,12] Bhat *et al.* reported an association between TM and autoimmune diseases.[16] 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

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	Vitamin B12 deficiency	Moderna	N/A	6 days	C2-5, T1	IVMP, oral-PSL, hydroxo-cobalamin	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	Tan *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	Miyaue *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	Unre-markable	None	Improvement
13	Sepahvand *et al.*, 2022 [13]	71	M	DM, HT, Heart disease	Sinopharm	1st	5 days	Medul-lary-C3	IVMP	Improvement
14	Roman *et al.*, 2021 [14]	N/A	N/A	N/A	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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