

Case Report

Acute longitudinal extensive transverse myelitis following the second dose of an inactivated COVID-19 vaccine: A case report of the youngest patient with post-Sinovac™ tetraplegia and poor prognosis

Hasan Hüseyin Gökpinar

Department of Physical Medicine and Rehabilitation, Kütahya Health Sciences University, Kütahya, Türkiye

ABSTRACT

During the novel coronavirus disease 2019 (COVID-19) pandemic, dozens of cases of acute transverse myelitis have been reported, either related to the disease itself or to various types of vaccines. However, rare cases of longitudinal extensive transverse myelitis (LETM) with relatively good prognosis have been reported, particularly after other COVID-19 vaccines, such as adenovirus vector vaccine (Oxford™, AstraZeneca), messenger ribonucleic acid (mRNA) vaccine (BioNTech™, Pfizer) and protein subunit vaccine (Corbevax™, Dynavax). This case report presents the third, worst prognosis and youngest case of LETM documented in the literature in association with an inactivated COVID-19 vaccine. A 39-year-old female patient developed sudden-onset severe cervical and thoracic predominantly paresthesia which rapidly progressed to tetraplegia, widespread sensory loss, bowel and bladder dysfunction two weeks after the second dose of Sinovac™ (Sinovac Biotech) vaccine. Spine magnetic resonance imaging showed LETM from C3 to T3 spinal cord segments. The outcome of this Sinovac™-induced LETM patient, who was inadequately treated with corticosteroids in the acute phase, showed a poor prognosis despite months of neurorehabilitation.

Keywords: COVID-19, intravenous immunoglobulin, plasmapheresis, Sinovac, steroid.

Vaccination has been documented as a rare cause of demyelinating diseases of the central nervous system, such as acute transverse myelitis (ATM). Examples include ATM cases which develop following vaccination against the hepatitis B virus, diphtheria, tetanus, and influenza.^[1] Longitudinal extensive transverse myelitis (LETM) is a subtype of transverse myelitis (TM) which extends along three or more subsequent vertebral segments.^[2] During the COVID-19 pandemic, many cases of TM and LETM have been described secondary to the COVID-19 infection.^[3,4] Furthermore, rare cases of ATM have been reported across almost all different types of COVID-19 vaccines.^[5-8] Additionally, new ATM and LETM cases associated with the administration of inactivated COVID-19 vaccines have been described in case reports from Pakistan,^[9] Iran,^[10] and Türkiye.^[11]

Demyelination disorders in the central nervous system, systemic inflammatory and autoimmune disorders, paraneoplastic syndromes and toxin/drug-induced or infectious etiologies are the other known causes of ATM.^[7] Despite all diagnostic evaluations, 60% of TM can still be idiopathic. Inflammatory LETM is also mostly idiopathic and may have a good prognosis with prompt and appropriate treatment.^[12] Treatments such as pulse methylprednisolone, intravenous immunoglobulin (IVIG) and plasmapheresis, particularly applied in the early stages, often provide satisfactory results. However, ATM still causes motor, sensory and autonomic dysfunction that leads to permanent and severe disability in one third of patients.^[13] Following COVID-19 vaccination, the most common mechanism underlying the development of adverse neurological symptoms appears to be

Corresponding author: Hasan Hüseyin Gökpinar, MD. Merkez Prime Hastanesi, Fizik Tedavi ve Rehabilitasyon Bölümü, 41400 Gebze, Kocaeli, Türkiye.

E-mail: hhg.gokpinar@gmail.com

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an immune-mediated response. Cross-reactivity and overactivity of the immune system and direct neurotoxicity have been suggested as etiopathogenic mechanisms. The immunological mechanism triggering autoimmunity may involve molecular mimicry, epitope spreading, cytokine upregulation, and polyclonal activation of B and T lymphocytes.^[14,15] Despite all these theories, the exact pathophysiological mechanisms and the causal role of the COVID-19 vaccine in the development of these neurological complications are still unclear.

Inactivated COVID-19 vaccines are those in which the virus is killed in a laboratory setting using traditional vaccine technology. These vaccines use inactivated virus particles to stimulate the immune system. Key examples include the Chinese-manufactured Sinovac-CoronaVac™ (Sinovac Biotech), which was used in Türkiye, BBIBP-CorV/Sinopharm used in Iran, the Russian-made CoviVac™, and the Indian-made Covaxin™. Due to their ability to generate stable immune responses similar to those of traditional vaccination methods, it has been believed, as an established expert opinion during the pandemic, that these vaccines might be less protective against COVID-19 compared to messenger ribonucleic acid (mRNA) and adenovirus vector vaccines, but could be relatively safer in terms of side effects. However, this case report demonstrates that unexpected and devastating outcomes, such as ATM, can also occur with inactivated vaccines. In this case report, the youngest and third Sinovac-induced LETM patient in the literature who was medically inadequately treated in the early period and showed inadequate recovery is reported.

CASE REPORT

A 39-year-old female healthcare worker presented to the Neurology Emergency Unit of Kütahya Health Sciences University on May 9th, 2021, with sudden-onset and severe burning pain, first affecting the upper back and subsequently the neck. This paresthesia was followed by a complaint of loss of sensory and severe weakness in all extremities, which first started in the upper extremities within minutes and rapidly spread to the lower extremities half an hour later. There was also urinary retention. The patient had no previously known disease or remarkable features in her rheumatological examination; however, although she did not contract COVID-19 during the pandemic period, she

received the second dose of the Sinovac™ vaccine approximately two weeks before her presentation. She had no comorbidities, and she previously had a body mass index (BMI) of 32 kg/m², but lost 18 kg voluntarily through dieting within the last year (BMI: 25 kg/m²). The polymerase chain reaction (PCR) test for COVID-19 was performed, and the result was negative. Upon cardiology and hematology consultations and detailed vasculitic and rheumatological examinations, no remarkable finding was detected. There was also no pathology in the requested brain magnetic resonance imaging (MRI). Anti-aquaporin-4 and myelin oligodendrocyte glycoprotein (MOG) antibodies were negative. According to the laboratory and cerebrospinal fluid parameters, brain MRI findings, and serology and autoantibody results, possible infection, vasculitis, tumoral lesion, Guillain-Barré syndrome-like polyneuropathy, multiple sclerosis, and neuromyelitis optica were excluded. The spine MRI taken revealed a syringomyelia-like lesion that was hyperintense in the T2 sequence and had diffuse contrast enhancement, which extended from the cervical C3 to the thoracic T3 level and was consistent with the LETM type of ATM (Figures 1 and 2). Almost all motor, sensory and autonomic components of spinal shock were present in the immobilized patient and spine MRI findings explained this spinal shock clinical picture. She was started on 1 g of



Figure 1. T1 + C sequence of cervical MRI (10.05.2021).

MRI: Magnetic resonance imaging; C: Contrast.

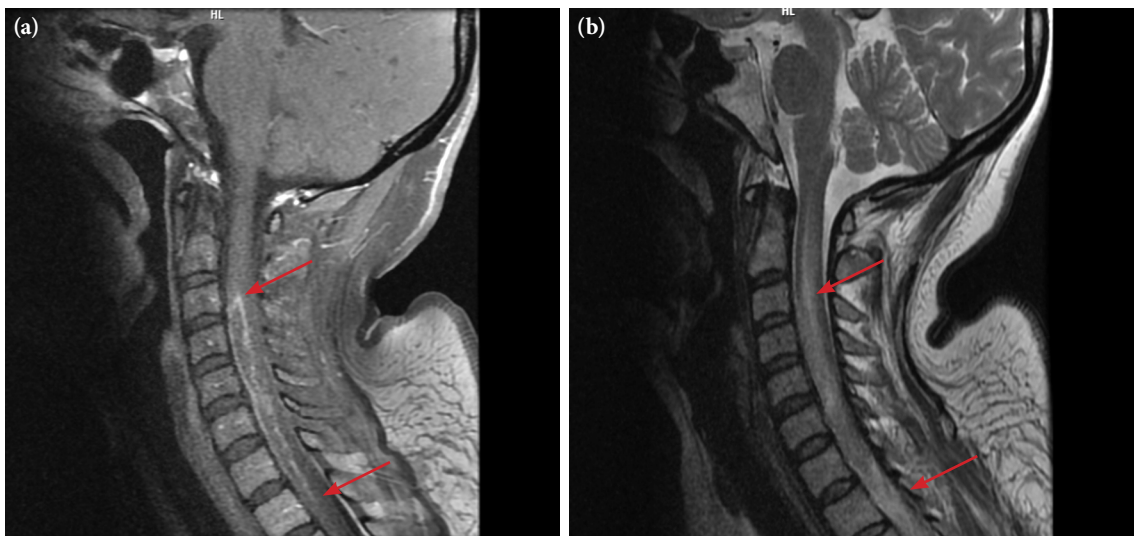


Figure 2. Magnetic resonance imaging showing (a) contrast enhancement and (b) hyperintensity of the acute longitudinal extensive transverse myelitis extending from the cervical C3 to the thoracic level (19.05.2021).

C: Contrast.

intravenous methylprednisolone at the neurology clinic, but steroids were discontinued on the second day due to fever and signs of infection. Treatments such as IVIG and plasmapheresis were not applied. Approximately one month later, she was transferred to the physical medicine and rehabilitation (PMR) clinic of the same hospital. As expected, the immobile patient with tetraplegia had upper motor neuron syndrome (UMNS) findings. The main ones were bilateral Babinski and Hoffman pathological reflex positivity, multi-beat clonus positivity detected more prominently in the left foot, increase in deep tendon reflexes, mild spasticity more prominent in the lower extremities, and severe muscle weakness causing more prominent paralysis in the left lower extremity and both upper extremities. The patient, who had no respiratory problems, came with a urinary catheter and had anal sphincter control. According to the modified Ashworth scale, the spasticity level was Stage 2 in the ankle plantar flexors and Stage 1+ in the right wrist and finger flexor groups. No significant spasticity was detected in other muscle groups. In the key motor muscle strength examination, right upper extremity C6 and C8 were 2/5, others were 1+/5, left upper extremity was 1/5, right lower extremity L2 was 2/5, L3 was 2+/5, distal was 2/5, left lower extremity L2 was 1/5, L3 was 1+/5, distal was 1/5. The patient with C3 neurological level had an American Spinal Injury Association (ASIA) Impairment Scale (AIS) Grade C motor incomplete and Functional Ambulation Category (FAC) level was 0. The patient

with neurogenic bladder for whom urodynamic evaluation was initially planned but could not be performed, clean intermittent catheterization (CIC) was initiated within a very short period. Oral treatment with gabapentin and a B1-B6-B12 vitamin complex was started due to neuropathic pain which began in the arms and legs following initial symptoms in the neck. To preserve the potentially beneficial effects of the mild spasticity, oral baclofen was not initiated during the early weeks but was introduced when the patient achieved ambulation at a FAC level 2. Botulinum toxin therapy was never required. The patient received neurorehabilitation for a total of around 5.5 months. Approximately two months after her hospitalization, she showed COVID-19 symptoms; therefore, the PCR test was requested. Due to a positive test result, the patient was transferred to the COVID-19 ward. She was never dyspneic or tachypneic throughout her hospital stay, and her pulse oxygen saturation level was consistently >93%, upon which the patient was taken back to the PMR ward. The patient underwent an intensive neurorehabilitation program consisting of virtual and robotic rehabilitation, manual stretching and strengthening exercises, instrumental agonist-antagonist concentric strengthening with hydraulic medical training equipment (Factum™, Frei Medical GmbH, Germany), balance-coordination and proprioception exercises with tramp trainer, and occupational therapy. Gradually, her muscle strength improved,

more on the right side, particularly in the lower extremities, and she ambulated with minimal physical assistance using a knee ankle foot orthosis (KAFO) on the left side and a solid ankle foot orthosis (AFO) on the right side. After a while, the patient was able to ambulate with a double-solid AFO under supervision. Although the balance problem was quite evident, the patient was far from being able to use an orthosis with her hands due to the weakness prevailing in the upper extremity. Therefore, being able to walk independently without using an orthosis was a very important goal and it was achieved. In the patient's follow-up examination of key muscle strength, right upper extremity C6 and C8 were 3/5, T1 was 1+/5, others were 2+/5, left upper extremity was 1+/5, right lower extremity L2 was 3/5, L3 was 3+/5, distal was 2+/5, left lower extremity L2 was 2+/5, L3 was 3/5, distal was 1+/5. The patient's ambulation level improved to FAC level 3. However, the patient's final ASIA grade remained unchanged and was again determined to be AIS C motor incomplete. After the urodynamic evaluation, CIC performed by the patient's spouse was continued. The patient was discharged six months after her hospitalization, discontinuing the use of AFO, notwithstanding our recommendation otherwise. Clean intermittent catheterization was discontinued under the supervision of a urologist during the post-discharge period. In the follow-up

MRI scans taken in the following months, with no contrast enhancement, the syrinx-like cavity in the lesion gradually decreased in parallel with the partial positive progression of the case (Figure 3). Currently, the patient has problems with balance disorder and dominant weakness in the upper extremities, can ambulate independently, although does not have the ideal gait pattern and final ambulation level is FAC 4. Due to the absence of bothersome spasticity, baclofen is not being used; however, the patient continues on pregabalin, which was initiated in place of gabapentin due to partially ongoing neuropathic pain. Written informed consent was obtained from the patient.

DISCUSSION

In the literature, the 39-year-old patient appears to be the youngest reported case of LETM associated with the administration of an inactive COVID-19 vaccine and exhibits the poorest prognosis. In the other two reported cases of LETM following inactivated COVID-19 vaccination, the patients were over 70 years of age.^[10,11] Other rare cases identified in the teenage and pediatric age groups were instances of LETM reported in association with mRNA or protein subunit active vaccines.^[15,16] This case of LETM with cervical and upper thoracic involvement developed in a young patient with no autoimmune history or comorbidities showed a severely involved and slowly recovering course. According to the literature, patients with ATM are typically in their 40s to 50s, and a large proportion of these patients have previous autoimmune diseases. The thoracic spine is the most frequently involved area.^[17] Most patients have a good prognosis, but being older, having received the second dose of a COVID-19 vaccine, and having a modified Rankin score of ≥ 3 are indicators of a poor prognosis.^[13] Although our patient was not elderly, the development of ATM two weeks after the second vaccination dose can explain the severe course of involvement and slow recovery, in line with the poor prognosis information in the literature. It is also worth mentioning that the majority of other vaccine-related ATM cases developed after the first dose, with a few cases occurring within two to three weeks following a second dose, as in our patient.^[7,11,18]

Since the involvement in our patients represented the LETM type of ATM that affects long sections and her modified Rankin score



Figure 3. Control cervical MRI showing the regressing involvement. T1 + C sequence (09.04.2022).

MRI: Magnetic resonance imaging; C: Contrast.

was ≥ 3 , this case can be considered an example of severe TM with a relatively poor prognosis compared to many previous post-COVID-19 ATM cases. In several similar cases, patients were able to ambulate within two to three weeks after high-dose steroids.^[2,5-7,18] In contrast, in our case, after months of immobility, ambulation was only possible under supervision, first with a KAFO and then with an AFO. Established UMNS findings, such as severe weakness and neurogenic bladder, affected the patient as serious sequelae for a long time. An important reason for this inadequate recovery may be that the high-dose steroids initiated were promptly discontinued on the second day due to an intervening infection. In a similar case report, despite the presence of an infection, high-dose steroids were continued with antibiotic therapy, and a more satisfactory recovery was observed.^[6] The fact that treatments such as plasmapheresis and IVIG, of which positive effects are mentioned in the literature, were not preferred may also explain the slow and limited recovery in the case.^[19] Although high-dose steroids constitute the primary treatment, a combination of IVIG, immunosuppressive agents, or plasma exchange may be needed in severe cases.^[17] In our patient, partial positive regressions in MRI findings were observed over a period of several months. Meanwhile, despite contracting COVID-19 approximately two months after the ATM attack, the patient's recovery from the infection without requiring oxygen support can be attributed to the immunization provided by the administration of two doses of an inactive vaccine. In this context, the patient paradoxically witnessed the bright and dark sides of vaccination together, regardless of the vaccine serotype.

Although studies have shown that ATM is more frequently associated with active COVID-19 vaccines, particularly the Oxford™ (AstraZeneca) vaccine (chimpanzee adenoviral vector-based), as well as mRNA-based vaccines such as Moderna™ (Moderna Inc.) and BioNTech™ (Pfizer), this case report and similar cases highlight the potential of inactivated COVID-19 vaccines, such as Sinovac™, to raise safety concerns regarding severe neurological complications such as ATM and LETM, regardless of age or comorbidity status.^[13,17] To minimize these safety concerns, proactive measures should be taken much earlier in future outbreaks similar to COVID-19, with a focus on developing safer vaccines. Specific corrective research efforts

should be intensified, particularly on risk-inducing parameters such as molecular mimicry between infectious antigens and self-antigens or adjuvants that can abnormally trigger antigen-specific innate and adaptive immune responses.^[7-9]

In conclusion, once the necessary differential diagnoses have been made and conditions such as ATM and LETM have been diagnosed, irrespective of whether the diagnosed condition is associated with vaccination, it is crucial to promptly initiate systemic anti-inflammatory treatments, particularly high-dose steroids, for adequate durations and immediately refer the patient to the PMR clinic for physical therapy.

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