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CASE REPORT

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Anaplastic Ependymoma and Atypical Refractory Longitudinal Expansive Transverse Myelitis Due to Immune Reaction After COVID-19 - A Case Discussion That Raises Many Unknown Questions About Covid-19

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ABSTRACT

Inflammatory neurologic manifestations, both infectious and non-infectious, have been reported secondary to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2/COVID-19). However, the relationship of spinal tumor and COVID-19 longitudinally extensive transverse myelitis (LETM) coexistence has never been reported in our knowledge. The clinical presentation and response to treatment of a 24-year-old female patient diagnosed with COVID-19 LETM and anaplastic ependymoma are described in this case report. The Patient's cerebrospinal fluid COVID-19 antibody level was higher than serum and she was resistant to immunosuppressive treatment. The interaction between COVID-19 and spinal tumor was discussed in the light of the literature. It is thought that COVID-19 infection could trigger tumor growth in this patient. Also, this is the first case of anaplastic ependymoma and COVID-19 myelitis coexistence in the literature.

Keywords: Anaplastic ependymoma, COVID-19, Longitudinal extensive transvers myelitis

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INTRODUCTION

There are still many unknowns about the coronavirus disease that affected the whole world. Neurological complications of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2/COVID-19) are among these unknowns. Inflammatory neurologic manifestations, both infectious and non-infectious, have been reported secondary to COVID-19 (1). Dysregulated immune reaction due to parainfection may cause antibody-mediated central nervous system (CNS) damage (2). In a review, authors reported 28/43 (70%) cases had longitudinally extensive transverse myelitis (LETM) (3). In the literature, there was no publication related to COVID-associated transverse myelopathy and spinal mass coexistence. In this case, such a patient will be reported and the relationship between COVID and mass will be discussed.

Highlights

- **Spinal mass with inflammatory myelitis due to mRNA COVID vaccine could coexist.**
- **To the best of our knowledge, this coexistence is reported for the first time in the literature.**
- **These two situations can worsen each other.**
- **An underlying glial tumor might progress rapidly in these patients.**
- **Further investigation should be performed to detect malignancy in such patients.**

CASE

A 24-year-old woman admitted to our hospital with progressive weakness of the lower limbs, and bladder dysfunction for one month. Some members of her household were tested positive for SARS-CoV-2 three months ago. A few days later she developed similar symptoms to other family members. She was vaccinated with BNT162b2 (Pfizer–BioNTech) one month later. In her history, she had low back pain for one year and constipation for 4 months.

In neurological examination, muscle strength of lower limbs was 0/5 on the left and 2/5 on the right. She had decreased sensation below Th10 level. Patellar and ankle reflexes were increased bilaterally. The plantar reflex was extensor on the left and absent on the right. She had a urinary catheter.

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There was hyperintensity in T2 weighted and Short-TI Inversion Recovery (STIR) in (MRI) images of the spinal cord from C1 to conus medullaris. Post-contrast images showed homogenous gadolinium enhancement of the lesion between thoracic (Th) 7 and Th11 levels. These MRI findings were evaluated as longitudinally extensive transverse myelitis (LETM) and a mass lesion of the spinal cord. Cranial MRI was normal.

The SARS-CoV-2 polymerase chain reaction (PCR) test was negative in the sera but the antibody test was positive (3.75 U/mL). Lumbar puncture (LP) was performed. Protein level in cerebrospinal fluid (CSF) was 672 mg/dl, there were 200 lymphocytes and no pathological cells. Acid-resistance bacteria and meningoencephalitis PCR panel were negative. COVID antibody level in CSF was 19.20 U/mL. Infectious parameters in serum were negative. There was no pathology in the vasculitic profile, B12, folate and tumor markers. There was not any distinctive pathology in protein and immunofixation electrophoresis. Peripheral smear, thorax and abdomen computed tomography, ultrasonography of lymph nodes, pelvis and mammography were evaluated as normal. Pathergy test was negative and absence of oral or genital aphthae excluded Neuro-Behçet's. Autoimmune encephalitis antibodies were negative. Anti-aquaporine4, anti-myelin oligodendrocyte glycoprotein (MOG) antibodies in serum and oligoclonal bands and anti-MOG antibodies in the CSF were negative. CSF immunoglobulin G index was normal. Visually evoked potential (VEP) was normal.

After a month from COVID-19 vaccination in addition to a possible COVID-19 infection, development of myelopathy was identified which suggests that the myelitis might be COVID-associated. The patient has been treated with 1000 mg/day intravenous methylprednisolone (IVMP) for seven consecutive days. After the treatment, clinical improvement was observed, but within a week her back pain returned and the muscle strength of lower limbs was 2/5 again. Spinal MRI was repeated and it was observed that the hyperintensity in the cervical spinal cord decreased to the T1 level after IVMP. But no regression was observed in the contrast-enhancing lesion in the thoracic spinal cord (figure 1). Before biopsy five courses of plasma exchange (PE) were administered every other day. Clinical improvement was observed again. Within ten days patient's clinic worsened again (Details are available in Figure 2).

Lumbar punction was repeated and again very high protein and moderate lymphocytic pleocytosis were detected. There was no atypical cell and pathology favoring infection. By the decision of the second council, intravenous immunoglobulin (IVIG), IVMP and one dose rituximab treatments were administered consecutively before the biopsy. Partial responses to treatments were observed, but the patient's clinic worsened each time after the effect of treatment wore off. The clinical and radiological temporal flowchart of the patient with treatments given during this period is described in Figure 3. In the latest MRI, despite the worsening in the clinical picture, it was observed that the hyperintense lesion size in T2 was almost equal to the enhancement lesion and the enhancement continued. Anaplastic cells were observed in biopsy pathology and reported as high-grade glial tumor (Figure 3). The lesion in the thoracic region was surgically resected. Anaplastic ependymoma was detected in the pathology.

DISCUSSION

In the presented patient, dramatic response to corticosteroid and PE, no atypical cells and lymphocytic pleocytosis in the CSF, no significant increase in the size of the contrast-enhancing lesion, and a higher COVID

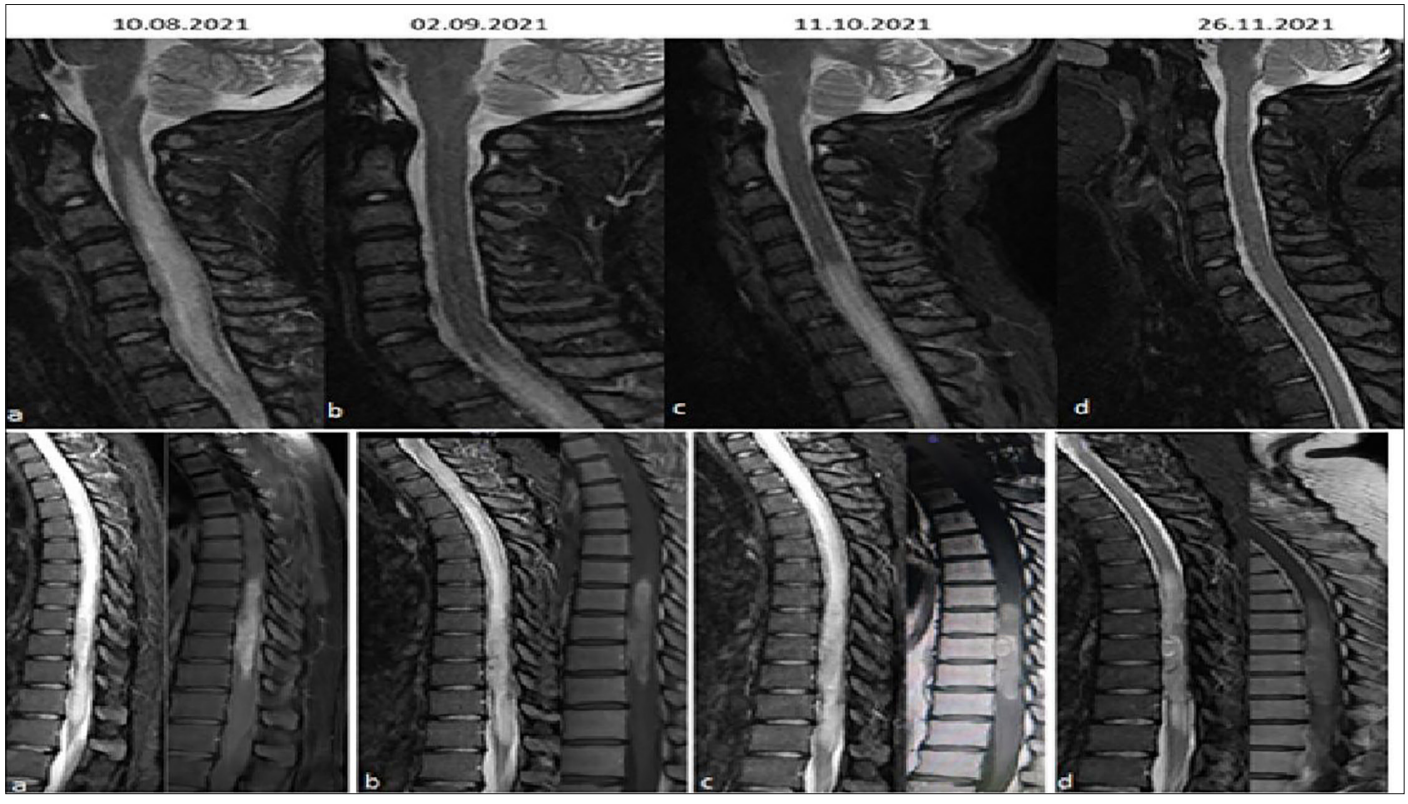

Figure 1. Radiological findings Show hiperintensity in Short-TI Inversion Recovery (STIR) in MRI images of the spinal cord from C1 to conus medullaris. Post contrast images showed homogen gadolinium enhancement of the lesion between Th7 and Th11 levels. Cervical and throcal spinal cord MRI STIR sequence shows hyperintensity from C1 to conus. Contrast enancment is seen in T7-11 level (1A-a). Cervical and throcal spinal cord MRI STIR sequence shows hyperintensity from C8 to conus. Contrast enancment is seen in T7-11 level (1A-b). Cervical and throcal spinal cord MRI STIR sequence shows hyperintensity from C7 to conus. Contrast enancment is seen in T7-11 level (1A-c). Cervical spinal cors is normal in STIR sequence. T7-11 contrast enhacment lesion and minimal perilesional eudoma is seen in throcal STIR and contrast+ images (1A-d). This MRI findings were evaluated as longitudinal extensive transverse myelitis (LETM) and a mass lesion of spinal cord. The temporal variation of the lesions over a 4-month period is shown.

August 2020	May 2021	July 2021	August 2021	September 2021	October 2021	November 2021
• Low pack pain+	• Low pack pain and constipation+	• Low pack pain and constipation.	• Transvers myelitis clinic+	• NE: Bilaterally LLMS: 2/5 (at 24 August 2021).	• After PE LLMS: +3/5, within one week LLMS worsened to 1/5.	• Within a week LLMS was 0/5 again.
• No radiological assesment.	• COVID-19 symptoms+ one month later the patient vacciated with Biontech.	• Outcenter throcal MRI-T2-hyperintense T7 11 lesion+	• NE LLMS: R: 0/5, L: 2/5	• MRI LETM from C8 to conus.	• MRI LETM from C7 to conus.	• 5 days IVIG and 500 mg rituximab+
	• No radiological assesment.	• Contrast-enhanced MRI was not performed in outcenter.	• MRI: LETM from C1 to conus (10.08.2021 fig. 1A-1).	• 22.09.2021- PE started (for five cures, 02.10.2021 finish).	• 5 days IVMP+ (after treatment LLMS was bilaterally 2/5).	• No clinical improvment seen.
			• IVMP for 7 days .			• MRI+only T7-11 lesion remained LETM not observed.
			• 18 August 2021 NE: bilaterally LLMS+4/5.			

Figure 2. Clinical and radiological temporal flowchart of the patient with treatments given during this period. MRI: magnetic resonance imaging, NE: neurological examination, LLMS: lower limb muscle strenght, R: right, L: left, LETM: longitudinally extensive transverse myelitis, IVMP: intravenous methilprednisolone, PE: plasma exchange, IVIG: intravenous immunoglobulin.

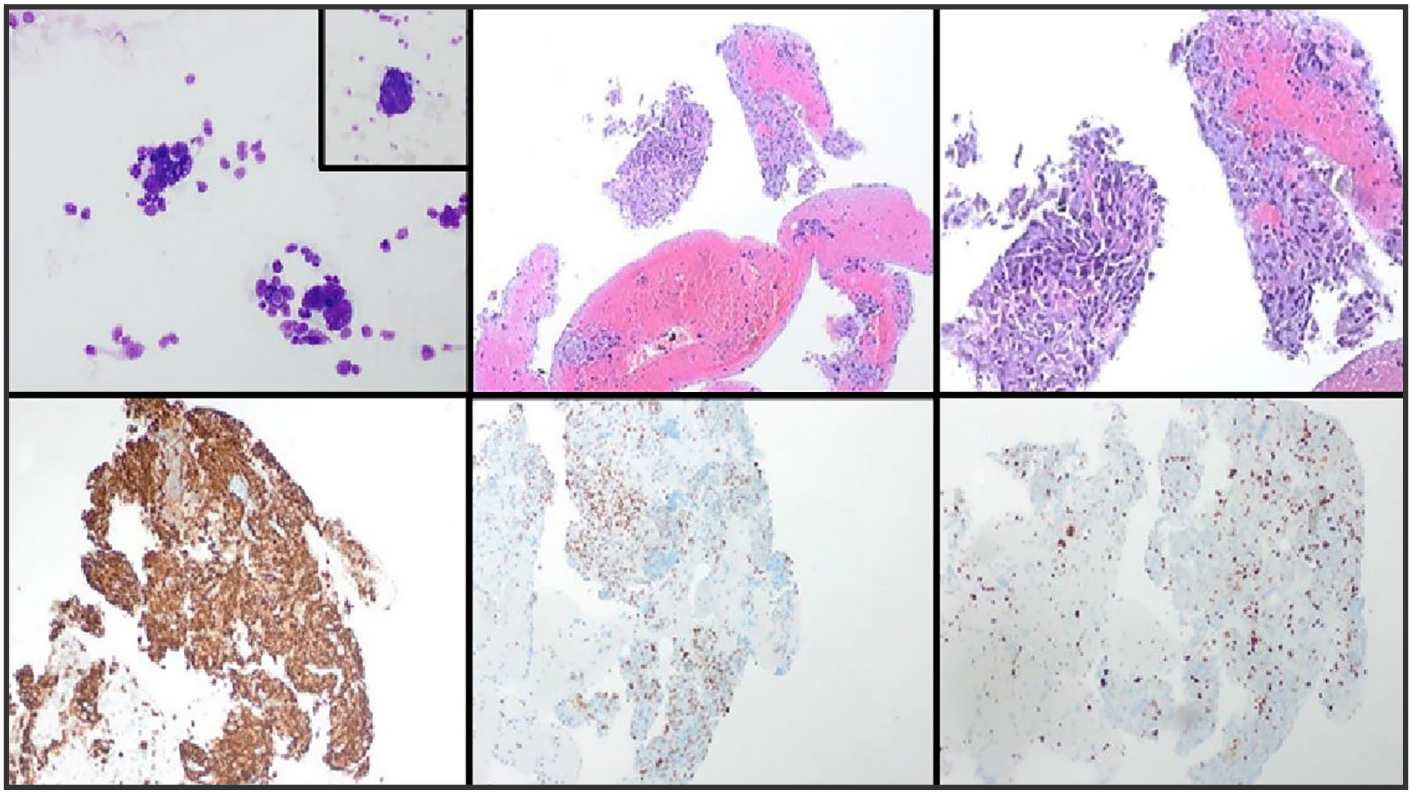

Figure 3. Highly anaplastic cells and one bizarre cell (insight) admixed with normal appearing ependymal cells (a); very tiny tissue fragments obtained within the same material reflecting a high grade malignant glial tumor (b and c, H&E, ×100 and ×200, respectively), proven by GFAP (d, DAB×200) and nuclear olig-2 (e, DAB×200) stainings with a high (up to 20%) Ki-67 proliferation index (f, DAB×200). As there are no immunoreactivity with EMA and CK AE1/AE3 and the proportion of olig-2 stained cells is high, a diagnosis of a grade 3 ependymoma is suggested.

antibody in CSF than in serum favor of myelitis, rapid worsening of the clinical picture after immunosuppressive treatments, too high protein in CSF, no regression in the enhanced lesion, and spread to the epidural space was evaluated in favor of the mass. In conclusion, the coexistence of mass and COVID-19 infection and/or mRNA COVID-19 vaccine-related inflammatory myelitis was considered in this case.

COVID-related inflammation has been linked to rapid neurological deterioration and tumorigenesis, and tumoral mass has been linked to the onset and severe progression of COVID-related myelitis. Only one article was found presenting with acute disseminated encephalomyelitis clinic and imaging after COVID mRNA vaccination (4). But in the follow-up the patient, glioblastoma multiforme was diagnosed. The susceptibility of cancer patients to infection due to immunosuppression is well known. In addition, the overexpression of SARS-CoV2 receptors and protease (ACE2, CTSL and TMPRSS2) significantly increased in many kinds of tumors, which facilitates viral entry into the cell and cancer patients more susceptible to SARS-CoV2 (5,6). So underlying tumoral mass may have triggered the COVID-19 infection to occur in the form of myelitis.

The most important factor that induces tumorigenesis is the microenvironment of the tumor. This microenvironment regulates all cancer hallmarks like angiogenesis, proliferation and multiple signaling pathways (7). In vulnerable cells signaling pathways could change due to overexpression of inflammatory substances such as cytokines (8). The most important of these signaling pathways are NF-kB and STAT pathways, which have also been shown to be activated by COVID-19 (9,10). It is suggested that COVID-19 S protein might have a binding affinity to epidermal growth factor receptors, vascular endothelial growth factor receptors and hepatocyte growth factor receptors in glioma cells (11). They speculate that COVID-19 can induce glioma tumorigenesis through the S protein, this may increase the risk of developing glioma in COVID-19 infected individuals and may amplify tumor growth in COVID-19 infected glioma patients (11). Although there was an improvement in the patient's clinic after immunosuppressant therapies during these four months, the change in inflammation did not fully explain the clinical change. Although the inflammation was almost completely resolved in the MRI images of the patient in November, her clinic remained paraplegic. It can be said that tumor growth is also effective in this case. However, with the patient's current findings, tumorigenesis as a hypothesis is still controversial and we think that further studies should be done to examine this phenomenon. Finally, to the best of our knowledge, the absence of anaplastic ependymoma and COVID-19 myelitis coexistence in the literature makes our case worth presenting. In conclusion, it should be considered that an underlying glial tumor may progress rapidly in patients with refractory neurological symptoms who have been infected with COVID-19 and whose CSF protein is very high. We suggest that further investigation should be performed to detect the presence of malignancy in such patients.

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