A Rare Case of Anti–Ma2 Antibody–Mediated Autoimmune Encephalomyelitis in Childhood

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A 9-year-old boy with no relevant previous medical history was admitted to our clinic following 9 days of persistent fever and headache, followed by generalized motor weakness and an altered state of mentality. The patient was initially evaluated by a primary care physician and treated with antibiotics, although no improvement was observed. On his first visit to our hospital, he displayed a confused mental state, signs of meningeal irritation, and decreased motor power (grades I–II) in all extremities on neurologic examinations. Laboratory tests, including thyroid function tests, level of immunoglobulin, and complements, were unremarkable. Brain and spine magnetic resonance imaging (MRI) showed T2 fluid-attenuated inversion recovery (FLAIR) high signal changes in the basal ganglia, thalami, corpus callosum, brainstem, cerebellum, and entire spinal cord with leptomeningeal enhancement (Fig. 1A). Electroencephalography revealed excessive delta slow-wave discharges throughout the entire record (Fig. 1B). Cerebrospinal fluid (CSF) analysis presented lymphocytic pleocytosis (360/μL, lymphocytes 94%, opening pressure 17 cmH2O), a high protein level (185 mg/dL), and a low glucose level (32 mg/dL). CSF bacterial culture was negative, as was a panel for herpes simplex virus, Epstein-Barr virus, and a FilmArray panel for meningitis/encephalitis. Due to a suspicion of infectious meningoencephalitis, antibiotics with acyclovir were used until negative confirmation in the infectious workup.

This research was approved by the Medical Sciences Ethics Committee of Asan Medical Center (IRB file No. 2020-1331). Written informed consent by the patients was waived due to a retrospective nature of our study.

During testing, his mental status progressed to a stupor without response to pain. According to the neurologic examination and tests, we empirically diagnosed autoimmune encephalitis (AE) and initiated 1 g of high-dose methylprednisolone (mPD) pulse therapy within 24 hours of the patient’s visit, and mannitol was used to control the increased intracranial pressure. On the third day of mPD pulse therapy, anti-Ma2 antibodies were detected in the serum, but not in the CSF. In contrast, other paraneoplastic antibodies, rheumatoid factor, antinuclear antibodies (ANA), dsDNA, anti-neutrophil cytoplasm antibodies (ANCA), aquaporin-4 (AQP4), anti-myelin oligodendrocyte glycoprotein (MOG), N-methyl-D-aspartate (NMDA), and anti-ganglioside antibodies were all negative. Considering the high risk of underlying malignancy in patients with anti-Ma2-associated AE, extensive tumor screening, including chest and abdomen computed tomography scans, testis ultrasonography, whole-body positron emission tomography–computed tomography, an ophthalmologic ex-
Fig. 1. (A) Brain and spine magnetic resonance imaging (MRI) (T2 fluid-attenuated inversion recovery [FLAIR]) at diagnosis show multifocal high signal intensity in both basal ganglia, thalami, cerebellum and brainstem, and diffuse longitudinally extensive hyperintensity involving the almost entire cord (yellow arrows in A). (B) Electroencephalography at diagnosis. (C) Brain and spine MRI (T2 FLAIR) at 5 months after onset.

amination, and echocardiography were performed; all showed no evidence of a tumor.

After consecutive treatment with intravenous immunoglobulin (IVIG, 2 g/kg, 4 days) and rituximab, the patient displayed some alert mentality with partial response. However, his quadriplegia present remained during day 7 of hospitalization. Additional plasmapheresis was performed, and his motor power in all extremities recovered to grades IV–V. After additional rehabilitation for 2 weeks, he could sit without assistance, stand with minimal support, and eat on his own.

Although bladder dysfunction and mild sleep disturbances remained, he was discharged from the hospital on day 25 with an annual follow-up schedule of neuroimaging and tumor screening. At a 5-month follow-up visit following disease onset, the boy could walk and lead a normal life without any significant neurologic disorders. Follow-up brain and spine MRI also showed a markedly decreased extent of T2 FLAIR high signal changes (Fig. 1C), despite persistently positive serum anti-Ma2 antibodies.

Here, we report a 9-year-old boy diagnosed with anti-Ma2-associated encephalomyelitis by a systemic screening for various auto-antibodies who was successfully treated with effective immunomodulation for this rare disease.

Anti-Ma2-associated encephalitis is a paraneoplastic immune-mediated disorder with preferential involvement of the lim-
Table 1. Summary of the reported pediatric anti-Ma2-associated encephalitis in pediatric patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Tumor</th>
<th>Initial symptoms</th>
<th>MRI findings</th>
<th>CSF findings</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mrabet et al. (2015) [2]</td>
<td>F/2 yr</td>
<td>Fever, headache</td>
<td>Increased T2 signal in left frontotemporal areas</td>
<td>Pleocytosis</td>
<td>Azathioprine</td>
<td>Partial recovery</td>
</tr>
<tr>
<td>Douma et al. (2021) [3]</td>
<td>M/8 yr</td>
<td>Behavioral disorder</td>
<td>Increased T2 signal in the external capsule</td>
<td>Normal</td>
<td>IVIG</td>
<td>Partial recovery</td>
</tr>
<tr>
<td>Douma et al. (2021) [3]</td>
<td>F/6 yr</td>
<td>Decreased mental status</td>
<td>Increased T2 signal in left temporoparietal, basal frontal, occipital areas</td>
<td>Pleocytosis</td>
<td>Azathioprine</td>
<td>Partial recovery</td>
</tr>
<tr>
<td>Douma et al. (2021) [3]</td>
<td>F/2 yr</td>
<td>Seizure</td>
<td>Increased T2 signal in right frontal areas</td>
<td>Normal</td>
<td>IVIG</td>
<td>Full recovery</td>
</tr>
</tbody>
</table>

MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; mPD, methylprednisolone pulse therapy; IVIG, intravenous immunoglobulin; ACTH, adrenocorticotropic hormone.

Consistent with our case, the initial reported symptoms of patients with anti-Ma2-associated encephalomyelitis are mainly changes in behavior and mental status, with or without a seizure. When there are only neurological symptoms and signs in children, it is difficult to differentiate between other inflammatory brain diseases; a strong clinical suspicion with extensive screening can provide an accurate diagnosis in our case and others. Although no evidence-based treatment protocols are currently available for pediatric AE, the first-line treatment often consists of high-dose steroids, IVIG, and/or plasmapheresis. Clinicians can escalate to second-line immunotherapy, including treatment with rituximab and cyclophosphamide, when first-line therapies have failed [6]. Anti-Ma2 antibody is not directly pathogenic, but indicates a T-cell-mediated immune response against neurons. High-dose steroid treatment is a favored option for immunosuppression over plasmapheresis in patients with classical onco-neuronal antibodies associated with AE due to primarily T-cell-mediated inflammation [7,8]. Considering the pathomechanism of anti-Ma2-associated encephalomyelitis, we administered high-dose steroids and IVIG as a first-line treatment. However, there was no response to these first-line therapies. Rituximab is a representative B-cell-depleting agent that can suppress T-cell activity by reducing B-cell-induced activation of T-cells. Unfortunately, we achieved only a partial response after administering rituximab as second-line therapy. Finally, we performed plasmapheresis to remove putative disease mediators, including toxic macromolecules and pathogenic antibodies [7,9]. Consequently, a significant improvement was achieved fol-
 Following 10 cycles of plasmapheresis.

We did not observe any evidence of an underlying paraneoplastic tumor with anti-Ma2-associated encephalomyelitis in our and other pediatric cases. There are no clear guidelines regarding how frequently or how long tumor screening should occur. However, according to other studies in adult patients, paraneoplastic neurologic disorders can be diagnosed before the detection of a tumor by up to 4 or 5 years. Therefore, we recommended annual tumor screening for at least 5 years with the imaging modalities, tumor markers, and clinical examinations due to the high-risk of malignancy in adult patients with anti-Ma2 encephalitis, despite the lack of specific evidence [2,10]. In our patient, at least 5 years of neurological follow-up and periodic screening have been initiated. A high index of suspicion and extensive autoantibody screening in a child with acute-onset encephalomyelitis could lead to an accurate diagnosis of anti-Ma2 encephalitis and prevent irreversible neurological sequelae with early appropriate therapeutic intervention. However, a standardized immunotherapy protocol and guidelines for tumor screening in pediatric patients are still under discussion. Additional large cohort studies are required to support evidence-based treatment protocols.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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