Unravelling Diagnostic Dilemma: AQP4-Positive Transverse Myelitis Mimics Spinal Intramedullary Tumor

To Editor,

Intramedullary spinal cord lesions can result due to varied etiologies such as: infection (tuberculosis, syphilis, viruses, fungal, bacterial), demyelination (acute transverse myelitis, multiple sclerosis-MS, neuromyelitis optica spectrum disorders-NMOSD, ADEM-acute demyelinating encephalomyelitis, MOG-associated-disorders), granulomatous disorders, vascular, syringomyelia, congenital abnormalities, and neoplastic lesions.[1] NMOSD is characterized by repeated attacks of optic neuritis and myelitis. The severity of the neurological deficit and the imaging characteristics may mimic intramedullary spinal cord tumor.[1] Hereby, we describe three patients of AQP4-positive NMOSD misdiagnosed as intramedullary tumor and operated.

Patient-1: A 32-year-old gentleman presented with three episodes of recurrent neurological disturbances between 2003 and 2010 that improved with steroids. In 2013, he developed progressive quadriparesis, MRI showed a C2-C3 intramedullary lesion [Figure 1]; possibility of an intramedullary tumor was considered and C1-C3 laminectomy was done. Histopathology was suggestive of demyelination, was treated with steroids. Between 2004 and 2013, he had five more episodes. Totally he had three episodes of optic neuritis and six episodes of myelopathy. He was referred to our institute in Nov 2014. During that time, his neurological examination revealed visual acuity of 6/60 in the right eye and complete blindness in the left eye. Spastic right hemiparesis with 4/5 power and mild distal weakness in left hand. Deep tendon reflexes (DTRs) were brisk in all four limbs with bilateral extensor plantars. His evaluation revealed positive serum AQP4 antibody. He was diagnosed as AQP4-positive NMOSD and started on azathioprine.

Patient-2: A 35-year-old lady presented with stiffness of both upper and lower limbs. MRI showed long segment expansile

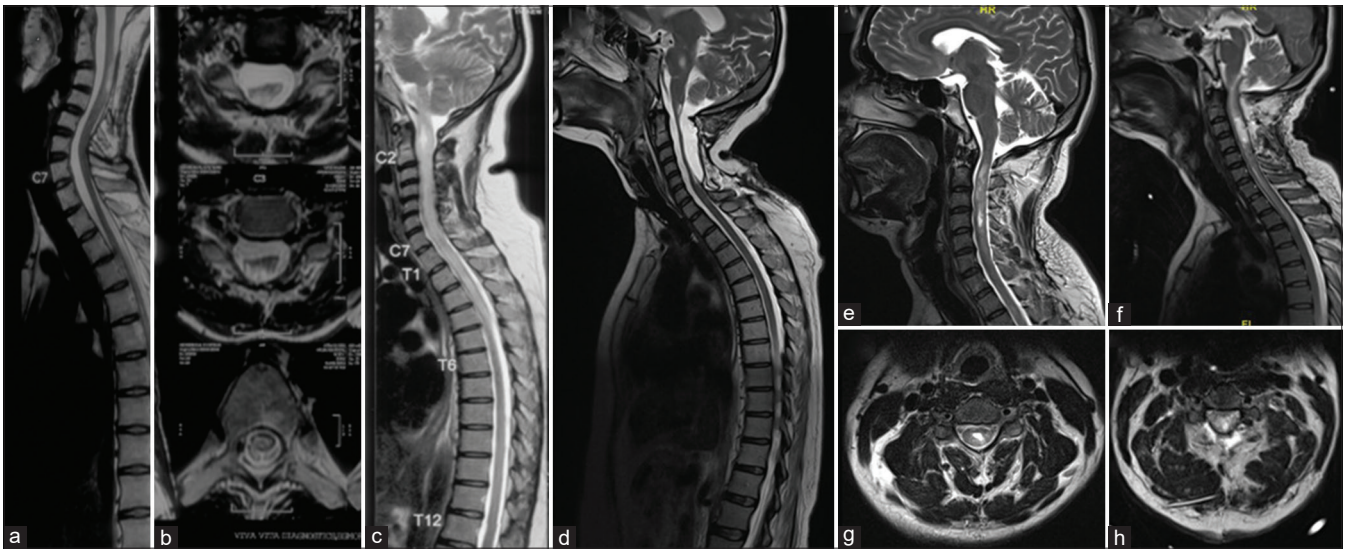

Figure 1: MRI findings of the patients. (a, b) MRI images of the Case-1. (a) Sagittal T2 sequence showing the atrophies operated cervical spinal cord across the C2-C3. (b) Axial images of the same showing atrophied cord with T2 hyperintensity involving more than 50% of the cervical cord. (c, d) MRI images of the Case-2. (c) Sagittal T2 sequence showing the MRI changes prior to surgery showing T2 hyperintensity of the cervical cord with edematous cord. (d) Sagittal T2 sequence of the same patient 6 months after the surgery showing the atrophied thinned out cervical cord with brainstem changes across the Pons. (e-h) MRI images of the Case-3. Sagittal T2 sequence pre (e) and Post-surgery (f). (g, h) Axial images of the cervical cord showing T2 hyperintensity with bright spotty lesion

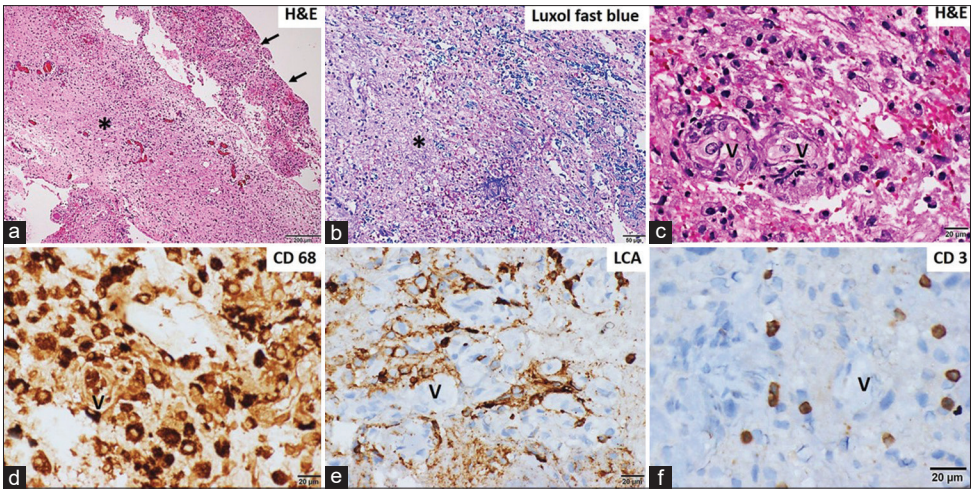

Figure 2: Pathological changes of the Case-3 patient. Cord parenchyma showing large none of pallor (*) surrounded by sheets of foamy macrophages (arrow, a). Luxol fast blue highlights the focus of demyelination (*) (b). Aggregates of foamy macrophages (c), labelled by CD68 (d) are seen aggregating around blood vessels, with admixed lymphocytes labelled by LCA stain (e), that are predominantly CD3 positive T lymphocytes (f). [Magnification = scale bar, V = vessel]

intramedullary lesion from medulla-T4 level [Figure 1]. The lesion was diagnosed as ependymoma/astrocytoma and she underwent C2–C6 laminectomy. Histopathology was suggestive of demyelinating disorder, serum was positive for AQP4 antibody. Post-surgery, she was subsequently evaluated by us. She had normal cranial nerve examination. Spasticity of all the four limbs with 0-1/5 power. DTRs were brisk with bilateral extensor plantars. She had decreased sensations below C5 with impaired vibration sense in the upper and lower limbs. She was treated with steroids, plasmapheresis, and Rituximab.

Patient-3: A 37-year-old farmer presented with progressive right-sided weakness of 15-days duration. Provisional diagnosis of C2-C5 intramedullary lesion- Pilocytic astrocytoma was made, C1-arch excision with C2-C4 laminectomy and spinal decompression was performed. Postoperative biopsy showed CD68-positive foamy macrophages suggestive of demyelination [Figure 2] following which was referred to us. He had normal cranial nerve examination. Spasticity of all the four limbs with 0/5 power. DTRs were brisk with bilateral extensor plantar response. He had decreased sensations below T2 with impaired vibration sense in the upper and lower limbs. He was diagnosed to have cervical myelopathy and evaluated. His serum and CSF AQP4-antibody were strongly positive. He was given steroids, plasmapheresis, and Cyclophosphamide.

All the patients in this case series had subacute onset of cervical myelopathy, were misdiagnosed as intramedullary neoplasm and were operated on. The first patient had steroid-responsive three episodes of recurrent neurological disturbances involving optic nerves and spinal cord. During the fourth episode he was suspected to have cervical cord ependymoma and operated. AQP4 was tested nearly 11 years after the onset of illness and diagnosed as NMOSD. The second and third patients had subacute onset of quadriparesis, both their MRI had shown T2-hyperintensity from cervicomedullary junction upto the cervical cord. Subacute onset, visual pathway involvement, recurrent neurological episodes, involvement of cervicomedullary junction on MRI and T2 bright spotty lesion on axial images were the diagnostic clues towards a demyelinating etiology.

There have been few cases previously where spinal cord lesions were suspected to be intramedullary tumors and operated. Brinar M *et al*.[2] reported five patients with spastic quadriparesis, biopsy was performed in two patients. The patients were diagnosed as NMO (1), MS (1), and ADEM (3). They found that demyelinating diseases involving the cord often exhibit the same clinical symptoms and signs as intramedullary tumors.[2] Oh SH *et al*.[1] reported a young female with bilateral upper limb weakness. Her MRI spine was suspected to be an ependymoma and a C2-6 laminectomy was done. Biopsy was suggestive of demyelination, serum AQP4 was positive suggestive of NMO. Habek M *et al*.[3] described a 43-year-old female patient with spastic quadriparesis. Spinal cord MRI revealed LETM (longitudinally extensive transverse myelitis) which was interpreted as a large intramedullary tumor. Biopsy revealed demyelination, serum was positive for NMO-IgG antibody.

Cohen *et al*.[4] reviewed spinal cord biopsies of 38 patients with progressive neurological deficits. MRI spine showed T2 hyperintense lesions in 92%, spinal cord expansion in 84%, and post-contrast patchy peripheral enhancement in 94%. Histopathology showed demyelination or sarcoidosis in 34%, spinal cord neoplasms in 21%, nonspecific changes in 26%, and one case each of TB and schistosomiasis. The treatment strategy was modified based on biopsy results in 26.3%.

It is important to clinically and radiologically distinguish demyelinating disorders from intramedullary spinal cord

Table 1: Comparison between NMOSD & intramedullary spinal cord tumor

Characteristics	NMOSD	Intramedullary Spinal Cord Tumor
Clinical Characteristics		
Gender	Common in Females	No Sex predilection
Onset of Neurological symptoms	Acute to Subacute	Subacute to Progressive
Monophasic/Relapsing	Monophasic or Relapsing Remitting.	Monophasic
Chronic/Progressive Course	Usually not present /Rare	Yes, Usually present
Optic Neuritis	Yes	No
Encephalopathy-ADEM-like	Yes	No
Cognitive dysfunction, Psychosis	Yes	No
Hypothalamic manifestations-Narcolepsy, anorexia, Hypersomnolence	Yes	No
INO-Internuclear Ophthalmoplegia	Yes	No
Area Postrema symptoms-hiccups, vomiting	Yes	No
Tonic spasms	Yes	No
Pruritus-Dermatological distribution	Yes	No
Investigation findings		
CSF	Normal/Elevated white blood cell count	Normal
CSF Protein (>45 mg/dL)	May be elevated	Usually Normal
CSF-Oligoclonal bands	Absent/Positive in 30%	Absent
IgG Index (>0.7)	Elevated	Normal
Serum-AQP4-IgG	Yes	No
MRI radiological features		
Location	Usually observed in cervical part of spinal cord. NMOSD has a predilection to affect cervical-medullary junction followed by cervical and then thoracic cord.	Ependymomas are usually situated in lower spinal cord around the conus Astrocytomas are more common in thoracic region
Involvement of cervicomedullary junction	Yes	No
Presence of bright spotty sign	Yes	No
Presence of hemorrhage	No	Yes
Presence of cyst formation	No	Yes
Peripheral patchy enhancement sparing the central grey	Yes	No
Associated brainstem and brain changes	Yes	No

NMOSD = Neuromyelitis optica Spectrum disorders; ADEM = Acute Disseminated Encephalomyelitis; CSF = Cerebrospinal fluid

tumors[5] as described in Table 1. Imaging studies in AQP4-NMOSD reveal T2-hyperintense, T1-hypointense LETM as the most typical spinal cord lesion with three or more contiguous vertebral segment involvement.[6,7] Cervical and thoracic cord are more frequently involved with preferential involvement of the central gray matter along the central canal of the spinal cord. When the cervical spine is involved, extension into the dorsal medulla/area postrema is commonly observed.[8] Apart from these, the presence of bright spotty lesions is a characteristic feature of AQP4-NMOSD. They are T2-hyperintense lesions on axial images, typically with higher signal intensity than that of the surrounding CSF.[6] Cord swelling and irregular enhancement is seen during the acute phase of AQP4-NMOSD on T1-weighted images, appearing as a combination of hypointense patchy areas and encasing ring-enhancing lesion resulting in a lens-shaped appearance on sagittal images.[7,8] This distinctive enhancement pattern can be used to differentiate AQP4-NMOSD from other causes of LETM.

In *Conclusion*, clinical presentation of neoplastic and non-neoplastic spinal cord lesions could be similar. Though MRIs could be characteristic in most of the cases, some pose a diagnostic dilemma. When in doubt, it is better to empirically treat the patient for a month with steroids and repeat imaging than considering invasive procedures. But, considering empiric steroids before biopsy should be the last approach after exhausting every possible option since it might confound the biopsy results, decrease the yield, further delay diagnosis and one might miss the window of opportunity to diagnose and hence potentially mistreat patients. Hence, Clinicians should be aware of the differences in clinical and imaging features of NMOSD and intramedullary spinal cord tumor.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients

understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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