

Paraneoplastic seropositive AQP4-IgG neuromyelitis optica spectrum disorder associated with sigmoid adenocarcinoma

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Abstract

Neuromyelitis optica spectrum disorder (NMOSD) is a relapsing demyelinating and inflammatory disease of the central nervous system, mediated by aquaporin-4 (AQP4)-immunoglobulin G (IgG) autoimmunity. Although NMOSD is most commonly an idiopathic autoimmune condition, it may also occur as a paraneoplastic syndrome in rare instances. Hereby, we report a rare case of a 61-year-old lady with paraneoplastic AQP4-IgG NMOSD associated with adenocarcinoma of sigmoid colon.

Keywords: Neuromyelitis optica spectrum disorder, transverse myelitis, sigmoid adenocarcinoma, paraneoplastic NMOSD, aquaporin-4 (AQP4)-immunoglobulin G (IgG) autoimmunity

INTRODUCTION

Neuromyelitis optica spectrum disorder (NMOSD) is an immune mediated disease of the central nervous system, where antibodies against the water channel protein aquaporin-4 is detected in approximately 80% of patients with this syndrome.¹ It is commonly an idiopathic autoimmune condition however there are a growing number of reports of NMOSD as a paraneoplastic phenomenon as well. Paraneoplastic neurological syndromes are remote immune-mediated effects of cancer, which can affect any part of the nervous system.

The two categories of antibodies against neural antigens are onconeural antibodies which nearly always indicate the presence of an underlying malignancy, or antibodies targeting surface antigens which are directly pathogenic.^{2,3}

We report a case of transverse myelitis as the presenting syndrome of NMOSD in association with sigmoid adenocarcinoma.

CASE REPORT

A 61-year-old Chinese female with nil significant past medical history presented with a 1-month history of paresthesia and numbness starting in her left upper limb and subsequently involved both lower limbs. She also reported loss of weight and

reduced appetite for the past 1 month associated with 1 week of vomiting. She did not complain of weakness in any limbs and there was no bladder or bowel incontinence. On systems review, there was no significant history of headache, neck pain or recent trauma. She had no history of recurrent oral ulcers, joint pains, or rashes. The patient had no history of smoking or alcohol consumption. She had no family history of autoimmune disorders or malignancy. On neurological examination, the patient was found to have reduced sensation to pinprick and light touch over the entire left upper limb and bilateral lower limbs up to mid shin. The tone and motor strength in bilateral upper and lower limbs were normal. Reflexes were largely normal (2+) across all limbs except for the left triceps and supinator reflexes which were reduced (1+). Joint proprioception and vibration were preserved. Examination of the cranial nerves was unremarkable, with no optic neuritis noted on eye examination. There were no cortical or cerebellar signs, and her gait was unremarkable. Digital rectal examination elicited peri-anal anaesthesia, with intact anal tone.

The patient underwent Magnetic Resonance Imaging (MRI) of the cervical and thoracic spine which showed long segment intramedullary T2w hyperintense signal and enhancement of C1 to T2 vertebral levels (Figure 1) and T4 to

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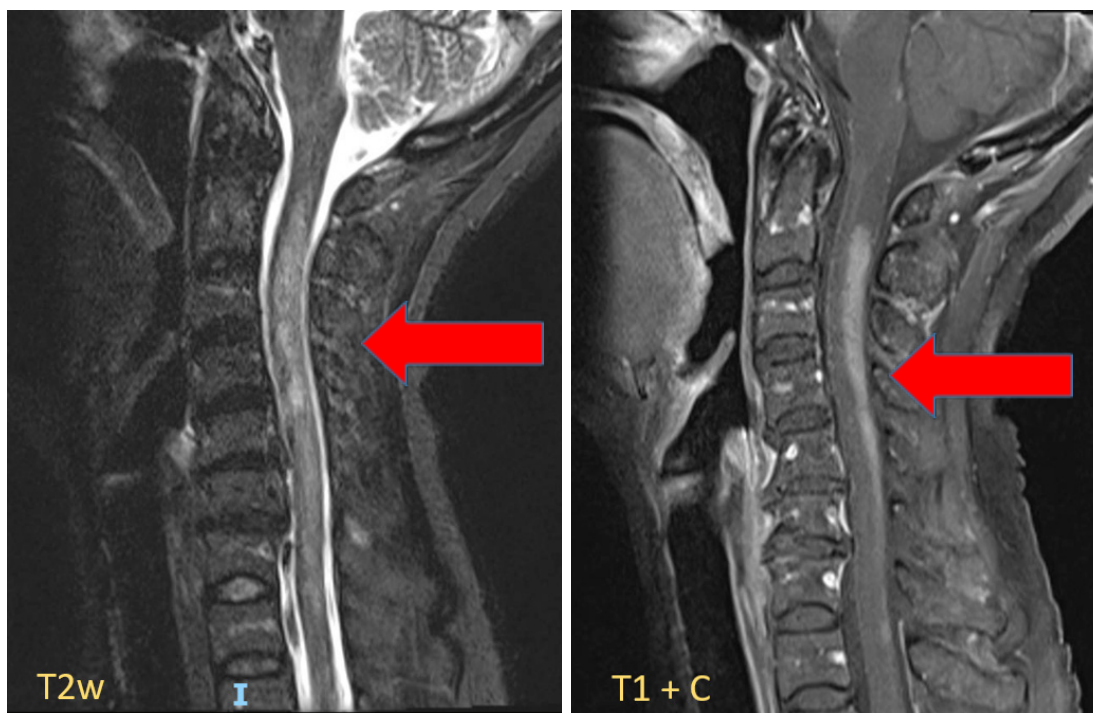


Figure 1. long segment intramedullary T2w hyperintense signal with post contrast enhancement preferentially affecting the dorsal aspect of the cervical cord from the C1 to T2 vertebral levels.

T7 (Figure 2). There was no enhancement noted in the lumbosacral spine. MRI Brain orbits with anterior visual pathway were unremarkable. Longitudinally extensive transverse myelitis from inflammatory, demyelinating, or paraneoplastic processes were then considered.

Comprehensive testing for other causes of transverse myelitis was undertaken, with the most significant result being the positive serum anti-aquaporin4 (AQP4 IgG), which in our Centre was performed via indirect immunofluorescence cell-based assay with cells transfected with AQP4 as substrate.

Other significant results were from the systemic autoimmune screen, which yielded positive Anti-nuclear antibody and anti-Ro. The rest of the extractable nuclear antigen (ENA) antibodies, as well as anti-double-stranded DNA were negative. Subsequent testing for possible Sjogren's was performed. Schirmer's test was positive which suggested possible Sjogren's syndrome and rheumatology referral was made for further follow up.

Other tests such as Vitamin B12, Folate, Thyroid Function and Erythrocyte Sedimentation Rate (ESR) were normal. Viral screening for Human immunodeficiency virus (HIV) and hepatitis were performed, of which HIV screen

was negative. The hepatitis B panel indicated past Hepatitis B infection with positive hepatitis B surface antibody and hepatitis B core antibody with undetectable hepatitis B DNA. Serum paraneoplastic antibody was also performed and returned negative.

Cerebrospinal fluid (CSF) studies showed slightly raised white blood cells (WBC) 8/uL with lymphocytic predominance of 91% and raised protein 0.77 g/L. CSF glucose 2.5 mmol/L was normal. CSF microbiological studies such as the meningitis multiplex PCR, gram stain, aerobic bacterial culture were negative as were CSF VDRL, acid-fast bacilli studies and fungal studies. CSF cytology was negative for malignant cells.

In view of her history of significant loss of weight, a CT thorax, abdomen, and pelvis was done which showed a short segment of colonic intussusception in the distal descending colon/proximal sigmoid colon, with suspicion of a mass as a lead point (Figure 3). A proximal sigmoid tumor about 3cm in size, half circumferential was noted on colonoscopy, with biopsy revealing adenocarcinoma. The patient subsequently underwent laparoscopic extended high anterior resection. Neurologically, she remained mildly symptomatic with only reduced sensation in the

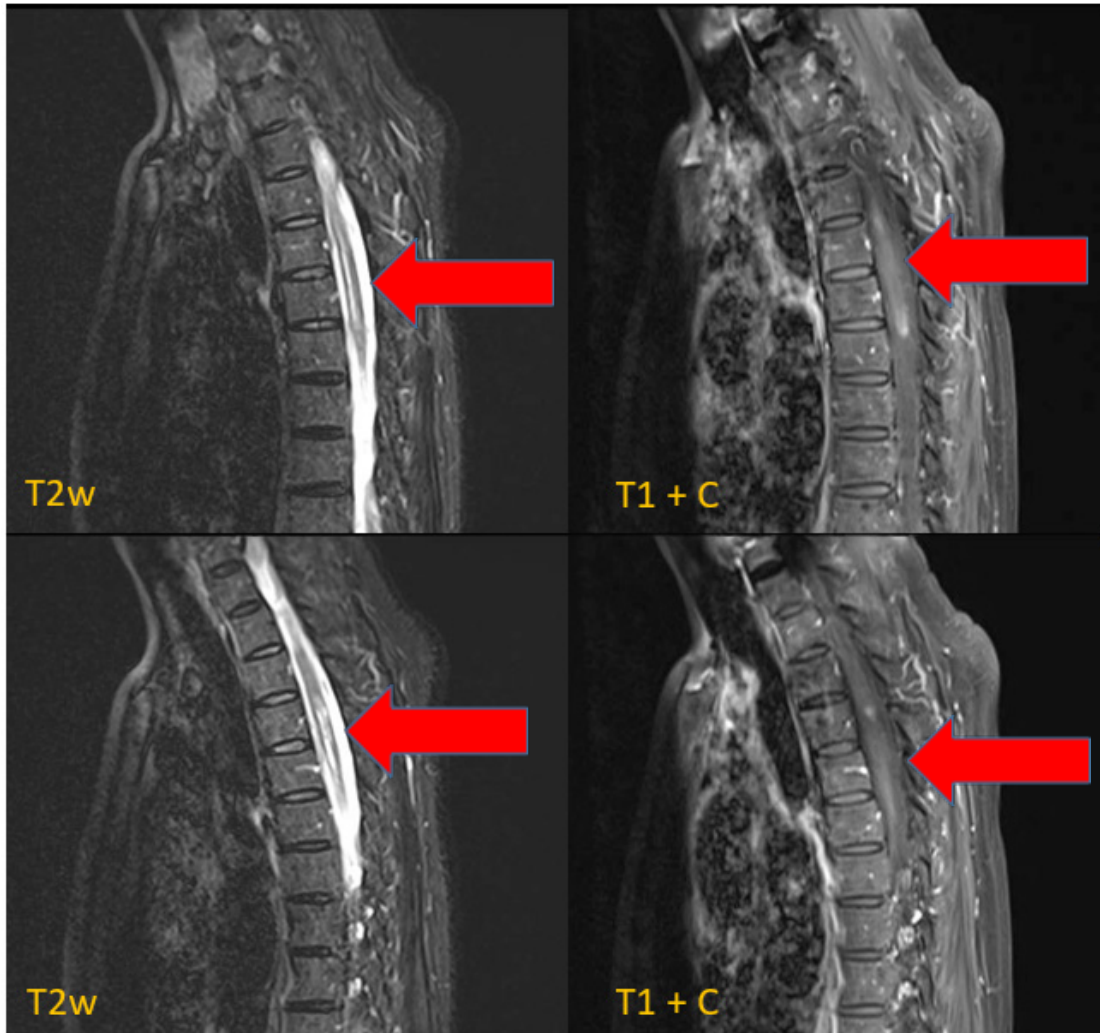


Figure 2. T2 hyperintense signal with post contrast enhancement from T4 to T7 vertebral levels.

left upper limb and bilateral lower limbs.

The patient was started on maintenance dose of oral steroids and mycophenolate mofetil with good neurological response.

DISCUSSION

Neuromyelitis Optica spectrum disorder (NMOSD) is a central nervous system (CNS) immune mediated demyelinating disease.⁴ It is driven by the presence of aquaporin-4 immunoglobulin G antibodies (AQP4-IgG) in most patients with NMOSD.

Paraneoplastic neurologic disorder (PNS) refers to a non-metastatic complication of cancer that can affect the central or peripheral nervous systems. PNS is proposed to be due to a triggering of the immune response from the expression of onconeural antigens on tumor cells.

Pittock *et al.* proposed that AQP4-IgG autoimmunity in some patients were tumor-initiated.⁵ AQP4 is the most abundant water channel found in the central nervous system, and has also been found in tumor tissue, including those from neurologically normal patients. Tissue expression for AQP4 is not found in all patients and tissue testing may not be available widely.⁶ The pathogenesis of paraneoplastic NMOSD remains poorly understood, with likely several factors required for inducing the production of AQP-4 IgG in patients with malignancies.

In contrast to many paraneoplastic autoantibodies that tend to be preferentially associated with specific cancers, AQP4-IgG has, so far, been found to occur in a variety of cancers. The most common malignancies that have been found to be associated with AQP4-IgG are breast and lung adenocarcinomas. However there have



Figure 3. Short segment of colonic intussusception in the distal descending colon/proximal sigmoid colon, with suspicion of a mass as a lead point.

also been reports of paraneoplastic NMOSD in cancers originating from the thymus, thyroid, ovaries, prostate and oesophagus, and in our case, the sigmoid.⁷⁻¹⁰

We report a case of transverse myelitis as the presenting syndrome of NMOSD in association with sigmoid adenocarcinoma. Even though our patient had serum AQP4 positive, given that sigmoid adenocarcinoma is a relatively common cancer occurring in people older than 50 years, testing tumour tissue for AQP4 would have solidified our possibility of our patient's NMOSD as being a truly paraneoplastic phenomenon. Unfortunately, tissue testing for AQP4 is not available at our centre and that is a limitation of our case report.

The frequency of individuals with NMOSD and underlying cancer is low. Nevertheless, there have been certain similarities and recurring patterns seen in these patients. A series of paraneoplastic NMO done by Sepulveda et al published in 2018 identified 2 parameters suggesting a higher risk of cancer: firstly patients who were along the older age spectrum and secondly, those presenting with

nausea and vomiting.⁸ Of note, AQP4 is reported to be highly expressed in the area postrema, an area of which there is a more permeable blood-brain barrier hence increasing the vulnerability of this region to an autoimmune attack.¹¹

Interestingly, our patient as described above had nausea and vomiting as part of her constellation of presenting symptoms, however she did not have any brainstem involvement seen on MRI. As shown in Figure 4, there was no signal change identified within the area postrema. Given the eventual diagnosis of colonic intussusception secondary to a sigmoid tumor, we presume her symptoms were more due to the local gastrointestinal effects of the tumor itself, rather than due to lesions within the area postrema. We also noted that on clinical examination she had diminished peri-anal sensation, despite no evident cauda equina involvement seen in the MRI. Converse to this as well, is the fact that she had preserved proprioceptive and vibratory senses, despite the presence of predominant dorsal column involvement on the MRI.

While NMOSD tends to cause rather severe

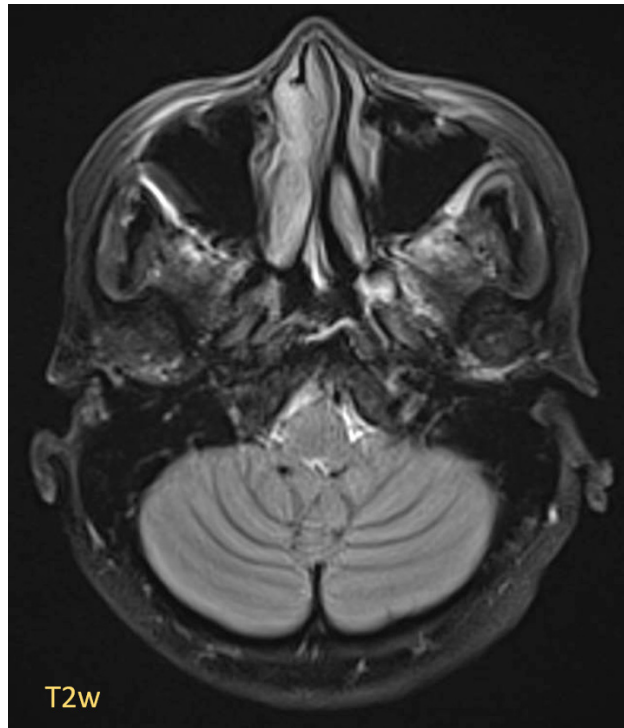


Figure 4. No signal abnormality within the area postrema

neurological symptoms, our patient was fortunate to have largely sustained only sensory symptoms despite the longitudinally extensive transverse myelitis seen on MRI. Due to the relatively mild symptoms, and the semi-urgent need to treat the cancer, she was started on oral steroids and mycophenolate mofetil without requiring intravenous methylprednisolone or plasma exchange. In addition, we proposed that treatment for NMOSD may potentially be discontinued if the cancer remained in full remission, with a negative repeat AQP-4 IgG test and provided the patient herself remained clinically well with no new radiological findings.

The other finding of note for our patient was the presence of anti-nuclear antibody and anti-Ro antibody. While she did not report any symptoms associated with Sjogren's, the Schirmer test was positive. Lip biopsy was offered to this patient however she declined further evaluation. The association of aquaporin-4 positivity with systemic autoimmunity, in particular with systemic lupus erythematosus and primary Sjogren's syndrome, has been frequently reported.^{4,12,13 12} The clinical significance of these autoantibodies in the absence of signs or symptoms however, remain unclear and is best to be followed up longitudinally.

While paraneoplastic NMOSD remains a

relatively rare occurrence, patients with NMOSD should be carefully screened for underlying malignancies, especially those of the older age group as well as those who present with symptoms such as nausea, vomiting, bowel dysfunction and weight loss.

As there remains much to be discovered on the pathogenesis and management of paraneoplastic NMOSD, there are many avenues for further studies, such as the clinical utility of AQP4 as an onconeural or paraneoplastic antibody. As it not widely reported that tumour cells have expression of AQP4, clinicians may also want to consider sending tumour tissue for testing of AQP4 depending on the availability of facilities. Additionally, for certain cancers such as in our patient with sigmoid adenocarcinoma it may be useful to repeat the serum AQP4-IgG to determine if the antibody remains detected after successful resection of the tumour. Longitudinal follow up is recommended to determine improvement or resolution of neurological symptoms.

DISCLOSURE

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Conflict of interest: None

Ethics: Informed written consent was obtained and documented. No ethics committee approval is required for case report publication as per our institutional policy.

REFERENCES

1. Waters PJ, McKeon A, Leite MI, *et al.* Serologic diagnosis of NMO: A multicenter comparison of aquaporin-4-IgG assays. *Neurology* 2012;78(9):665-71. doi:10.1212/WNL.0b013e318248dec1
2. Graus F, Saiz A, Lai M, *et al.* Neuronal surface antigen antibodies in limbic encephalitis: Clinical-immunologic associations. *Neurology* 2008;71(12):930-6. doi:10.1212/01.wnl.0000325917.48466.55
3. Zhang H, Zhou C, Wu L, Ni F, Zhu J, Jin T. Are onconeural antibodies a clinical phenomenology in paraneoplastic limbic encephalitis? *Mediators Inflamm* 2013;2013:1-9. doi:10.1155/2013/172986
4. Wingerchuk DM, Banwell B, Bennett JL, *et al.* International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology* 2015; 85(2):177-89. doi: 10.1212/WNL.0000000000001729
5. Pittock SJ, Lennon VA. Aquaporin-4 autoantibodies in a paraneoplastic context. <http://archneur.jamanetwork.com/>
6. Apiraksattayakul N, Songwisit S, Owattanapanich W, *et al.* AQP4-IgG-positive neuromyelitis optica spectrum disorder and temporally detected neoplasms: case report and systematic review. *Mult Scler Relat Disord* 2022; 68:104212. doi: 10.1016/j.msard.2022.104212.
7. Ding M, Lang Y, Cui L. AQP4-IgG positive paraneoplastic NMOSD: A case report and review. *Brain Behav* 2021;11(10). doi:10.1002/brb3.2282
8. Dinoto A, Bosco A, Sartori A, *et al.* Hiccups, severe vomiting and longitudinally extensive transverse myelitis in a patient with prostatic adenocarcinoma and Aquaporin-4 antibodies. *J Neuroimmunol* 2021;352:577488. doi:10.1016/j.jneuroim.2021.577488
9. Sepúlveda M, Sola-Valls N, Escudero D, *et al.* Clinical profile of patients with paraneoplastic neuromyelitis optica spectrum disorder and aquaporin-4 antibodies. *Mult Scler* 2018;24(13):1753-9. doi:10.1177/1352458517731914
10. Bahnasy WS, Ragab OAA, Eissa AAN. Neuromyelitis optica as a paraneoplastic manifestation of bronchogenic carcinoma: A case report. *J Neurol Exp Neurosci* 2019;5(2):76-9. doi:10.17756/jnen.2019-058
11. Popescu BF, Lennon VA, Parisi JE, *et al.* Neuromyelitis optica unique area postrema lesions: nausea, vomiting, and pathogenic implications. *Neurology* 2011; 76(14):1229-37. doi: 10.1212/WNL.0b013e318214332c.
12. Martín-Nares E, Hernandez-Molina G, Fragosoloy H. Aquaporin-4-IgG positive neuromyelitis optica spectrum disorder and systemic autoimmune diseases overlap syndrome: a single-center experience. *Lupus* 2019;28(11):1302-11. doi:10.1177/0961203319877255
13. Park JH, Hwang J, Min JH, Kim BJ, Kang ES, Lee KH. Presence of anti-Ro/SSA antibody may be associated with anti-aquaporin-4 antibody positivity in neuromyelitis optica spectrum disorder. *J Neurol Sci* 2015;348(1):132-5. doi:https://doi.org/10.1016/j.jns.2014.11.020