

# Neuromyelitis Optica as a Paraneoplastic Manifestation of Bronchogenic Carcinoma: A Case Report

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**Received:** August 05, 2019

**Accepted:** November 01, 2019

**Published:** November 04, 2019

**Citation:** Bahnasy WS, Ragab OAA, Eissa AAN. 2019. Neuromyelitis Optica as a Paraneoplastic Manifestation of Bronchogenic Carcinoma: A Case Report. *J Neurol Exp Neurosci* 5(2): 76-79.

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## Abstract

**Context:** Neuromyelitis optica spectrum disorders (NMOSDs) are an autoimmune disorders resulting from astrocytic aquaporin-4 (AQP-4) channelopathy in young adults. The AQP-4 IgG antibodies may be present in the context of some paraneoplastic disorders which should be suspected when NMOSD occur in elderly patients.

**Findings:** This study reported a case of 65-year-old male patient with paraneoplastic NMOSD. The patient presented with quadriparesis due to acute cervical long segment myelitis not responsive to pulse steroid therapy; 18 months later he developed acute bilateral diminution of visual acuity due to bilateral optic neuritis with no response to either pulse steroid therapy or IVIG. Serological serum tests revealed that the patient was AQP-4-IgG positive, but after 22 months of the initial presentation, the patient showed widespread metastasis in bone and liver secondary to bronchogenic carcinoma.

**Conclusion:** Late onset of NMOSD should raise the suspicion of paraneoplastic neurological disorder, and extensive work up is advised to identify the underlying neoplasm.

## Keywords

Neuromyelitis optica spectrum disorder, Devic's disease, Paraneoplastic, Aquaporin-4, Bronchogenic carcinoma

## Abbreviations

**AQP-4:** Aquaporin-4; **IVIG:** Intravenous Immunoglobulin; **NMOSD:** Neuromyelitis Optica Spectrum Disorder; **ON:** Optic Neuritis; **TM:** Transverse Myelitis

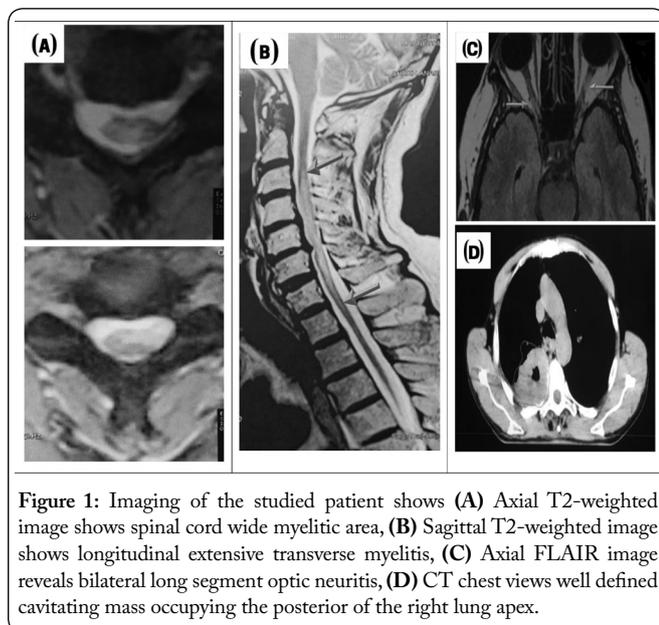
## Introduction

Neuromyelitis optica spectrum disorders (NMOSDs) are a severe autoimmune inflammatory demyelinating disorders of the central nervous system (CNS) affecting young adults. It typically presents as monophasic or relapsing optic neuritis (ON) and longitudinally extensive transverse myelitis (LETM). The AQP-4 are the most abundant water channel subtype in the CNS and are highly represented in the astrocytes [1]. Circulating IgG autoantibodies targeting the AQP-4 channels are present in the serum of most cases, the levels of which are correlated with the clinical severity of the disease [2]. When the

autoantibodies cross the blood brain barrier, they attack the astrocytes water channels with a resultant astrocytic loss through complement mediated cytotoxicity. This extensive astrocytopathy results in loss of the astrocytic trophic support to oligodendrocyte in specific CNS regions with subsequent apoptosis, demyelination and finally axonal loss [3].

## Case Description

Sixty-five-year-old male patient with history of hypertension and significant smoking (smoking index: 60) presented with an acute onset of quadriplegia most apparent in the left side associated with an acute urine retention and constipation. Clinical examination revealed the presence of myelitic picture with a tendency to Brown-Séquard Syndrome. MRI cervical spine showed LETM segment affecting the 3<sup>rd</sup> to the 7<sup>th</sup> cervical spinal cord (Figure 1A). Cross MRI sections showed that; the patch was predominantly paracentral and affected more than 50% of the spinal cord segments (Figure 1B). Brain MRI showed mild periventricular white matter hyperintensities and the CSF analysis revealed mild increase in proteins (54 mg/dl) and white blood cell count (12 cell/mm<sup>3</sup> predominantly lymphocytes). The patient underwent an autoimmune battery of investigations including; LE cells, ANA, ANCA, anti-dsDNA, anti-SS-A and anti-CCP antibodies which were normal. The patient was diagnosed as a case of acute monophasic transverse myelitis and consequently received pulse steroid therapy (1-gram methyl prednisolone IV for 7 consecutive days) with very minimal improvement where he became wheel chair dependent with repeated indwelling Foley's catheter.



18 months later, the patient developed acute bilateral severe diminution of vision with MRI showing long segments of bilateral optic neuritis which were largely posterior in the right side (Figure 1C). The patient received another course of pulse steroid therapy with no improvement. Serum AQP-4

antibodies was ordered and it showed elevated titer (132 unit/ml) which led to the diagnosis of NMOSD, and hence IVIG was given, but unfortunately; there was no improvement in either motor, sphincter or visual deficits.

22 months after the initial presentation, the patient developed profound weight loss, cough, dyspnea with CT chest showing well defined cavating mass occupying the posterior of the right lung apex encasing the aorta, biopsy revealed non-small cell bronchogenic carcinoma (Figure 1D). The CT abdomen and MRI dorsal vertebral spine showed extrapulmonary metastatic spread. The patient's general condition rapidly deteriorated and developed respiratory failure. The patient was placed on mechanical ventilation, and unfortunately he died as a result of cardiac arrest.

## Discussion

Paraneoplastic neurological syndromes (PNSs) are disorders associated with cancers and they are not caused by direct invasion, metastasis, malnutrition or consequences of treatment, but they result from the immunological reactions to the tumor [4]. Neuromyelitis optica is an autoimmune inflammatory disorder of the CNS associated with serum as well as cerebrospinal AQP-4 antibodies [5].

The reported case fulfilled the international panel for NMO diagnostic criteria [6] through the presence of 2 core clinical characteristics (optic neuritis and LETM) in addition to the highly specific AQP4-IgGp positive test.

The initial presentation with cervical LETM (which was more or less affecting the white matter more than the grey matter) without any other central nervous system region affected, didn't draw our attention to the diagnosis of NMOSD at that time. The vascular etiology was excluded, as the clinical picture and the MR imaging eliminated the possibility of anterior spinal artery occlusion; moreover, the CSF analysis didn't support the diagnosis of infective myelitis. Based on these findings and the negative serology of other systemic autoimmune disorders (SLE, rheumatoid arthritis Sjögren's Syndrome or vasculitis), our decision was to initiate pulse steroid therapy, which resulted in poor improvement in the patient's case. Through one and a half year of that myelitis episode, the patient developed optic neuritis. At that point, we shifted our diagnosis to the possibility of NMOSD, which has been confirmed by the positive serology for AQP-4 antibodies. With the presence of massive pleural effusion, bone, liver metastasis and bronchogenic carcinoma raised the possibility that the NMOSD was a prodromal PNSs of this tumor.

Pittock et al. [7] reported several types of neoplasms in patients with NMOSD, including breast carcinoma, thyroid, B-cell lymphoma and pituitary. They proposed that neoplastic cells may express onconeural antigens that can trigger an AQP-4 immune response.

Ontaneda and Fox [8] reported that up to 15% of patients with seropositive AQP-4 antibodies NMOSD had a history of neoplasm, and the neurological manifestation of NMOSD

may precede or follow the diagnosis of neoplasm. Anti-AQP4 immunoreactivity was found in non-small cell lung cancer with the highest expression levels to be present in well differentiated adenocarcinoma [9].

Kobata et al. [10] reported another case of paraneoplastic NMOSD secondary to lung adenocarcinoma. The patient presented with cerebellar ataxia and intractable vomiting. She underwent partial pulmonary resection, and received intravenous steroids and plasma exchange which improved her neurological deficits.

Interestingly, paraneoplastic NMOSD has been associated with collapsing response-mediator protein 5 (CRMP5/anti-CV2) antibodies and amphiphysin antibodies in patients with small cell lung carcinoma, thymoma and renal cancer [11].

In our reported case, the time from the initial presentation till final diagnosis of paraneoplastic NMOSD was 22 months; it was similar to that time reported by Beauchemin [12] in his case series (ranging from 3 to 48 months).

One of the drawbacks of the management of our case is latent in the fact that we didn't suspect NMOSD as a provisional diagnosis at the initial presentation. The second one was not considering the possibility of paraneoplastic disorder after NMOSD diagnosis had been confirmed.

However, the management of paraneoplastic NMOSD is not straightforward. We think the disease course in our patient would have been modified, if he had been diagnosed at the initial presentation as a paraneoplastic NMOSD.

Early detection of neoplasm could permit its surgical resection, then immune-modulatory therapies such as Eculizumab (monoclonal IgG that neutralizes the complement protein C5 and prevents its cleavage into C5a, which is proinflammatory, and C5b, which coordinates the formation of membrane attack complex) or Tocilizumab, (humanized anti-interleukin-6 receptor antibody), as elevated serum levels of IL-6 promote plasmablasts survival and AQP4-IgG synthesis, in addition to that; these medication have antineoplastic effect on different neoplasms including bronchogenic carcinoma [13].

Paraneoplastic NMOSD are more frequently affecting older male patients, and usually presented with brain stem symptoms associated with severe nausea and vomiting with similar response to steroid therapy as non-paraneoplastic NMOSD, however; patients with paraneoplastic NMOSD had more relapses with early deaths as a consequence of cancer complication [14].

Dutra et al. [15] as well as Annus et al. [16] stated that late onset of NMOSD after the age of 50 should raise the suspicion of paraneoplastic disorders. This assumption was reinforced by the work of Cai et al. [11] who found that half of patients with paraneoplastic NMOSD were over 50 years, compared with only 16% of patients with non-paraneoplastic NMO. In other words, NMOSD, is more likely to be paraneoplastic in patients aged over 50 years at the onset of symptoms.

Finally, we hope that our present case could help to

recognize NMOSD in old age as a paraneoplastic disorder which in turn will result in early detection of underlying cancer and consequently proper management of those patients.

## Conclusion

We report a case of old male patient presented with an acute cervical long segment myelitis not responsive to pulse steroid therapy; later he developed an acute bilateral optic neuritis not responsive to either pulse steroid therapy or IVIG. The patient was diagnosed as a case of NMOSD and he showed widespread metastasis secondary to bronchogenic carcinoma.

This case report gives an extra evidence to the current literature of considering the possibility of paraneoplastic etiology of NMOSD in elderly patients. Early detection of underlying cancer may lead to a proper management and in turn will result in better prognosis.

The work was carried out in The Neuropsychiatry Department, Tanta University Hospitals, Tanta, Egypt.

## Consent of Publication

The patient's son had signed an informed consent to participate and for the data to be published.

## Conflict of Interest

All authors have no competing interests related to the study.

## Availability of Data and Materials

The datasets used and/or analyzed during the current study are available on reasonable request.

## Funding Source

No funding has been received.

## Acknowledgments

We would like to thank Dr. Ahmed Mohammed Abozeid Abdo; the patient's son for his great help in providing the data and investigations of his late father. Finally, we should thank Mrs. Hagar Aboelfath for her help in editing this manuscript.

## Authors Contributions

All the authors contributed equally in the patient's examination and follow-up, the study's idea and design, patient's data and references collection, manuscript writing, revision and final approval.

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