

**Case  
Report**

# Paraneoplastic Neuromyelitis Optica Spectrum Disorder Associated with Atypical Thymic Carcinoid: A Case Report

Suguru Mitsui, MD,<sup>1</sup> Yugo Tanaka, MD, PhD,<sup>1</sup> Kenji Kimura, MD,<sup>1</sup> Naoe Jimbo, MD, PhD,<sup>2</sup> Norio Chihara, MD, PhD,<sup>3</sup> and Yoshimasa Maniwa, MD, PhD<sup>1</sup>

**Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune inflammatory disease, occasionally accompanied by malignant tumors. Immunosuppressive therapy is the mainstay treatment for idiopathic NMOSD; no guidelines have been published for paraneoplastic NMOSD because it is rarely reported in the literature. We report a rare case of a 67-year-old man with paraneoplastic NMOSD associated with thymic carcinoid whose cells expressed aquaporin-4 antibody. After surgical resection, the patient's symptoms improved, and serum aquaporin-4 autoantibody turned negative. We believe that radiographic examination for mediastinal tumors in patients with NMOSD is necessary because thymic epithelial tumors could have a role in the pathogenesis of paraneoplastic NMOSD. After mediastinal tumor has been detected, they should be surgically resected to improve neurological symptoms.**

**Keywords:** paraneoplastic syndrome, thymic cancer, thymothymectomy

## Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune inflammatory disease, characterized by severe optic neuritis, longitudinally extensive myelitis, and serum expression of aquaporin-4 autoantibodies, which can cause neuroinflammation.<sup>1)</sup> NMOSD is

occasionally accompanied by malignant tumors, and several reports have mentioned the possibility that those tumors produced aquaporin-4 autoantibodies, which may have initiated the autoimmune response.<sup>2)</sup> Immunosuppressive therapy is the mainstay treatment for idiopathic NMOSD; no guidelines have been published for paraneoplastic NMOSD because it is rarely reported, and few reports have confirmed that aquaporin-4 autoantibodies are produced by the tumor cells. We report, for the first time, a case of paraneoplastic NMOSD associated with thymic carcinoid whose cells expressed aquaporin-4 antibodies, in which the symptoms improved after surgery.

## Case Report

A 67-year-old man presented with sudden-onset left-sided vision impairment and persistent hiccups that had lasted 1 month. Neurological examination showed left-sided relative afferent pupillary defect, gaze-evoked nystagmus, and dysarthria. Magnetic resonance imaging (MRI) of the brain and spinal cord showed abnormal T2-weighted hyperintensity of the brain stem, occipital

<sup>1</sup>Division of Thoracic Surgery, Kobe University Graduate School of Medicine, Kobe, Hyogo, Japan

<sup>2</sup>Department of Diagnostic Pathology, Kobe University Graduate School of Medicine, Kobe, Hyogo, Japan

<sup>3</sup>Division of Neurology, Kobe University Graduate School of Medicine, Kobe, Hyogo, Japan

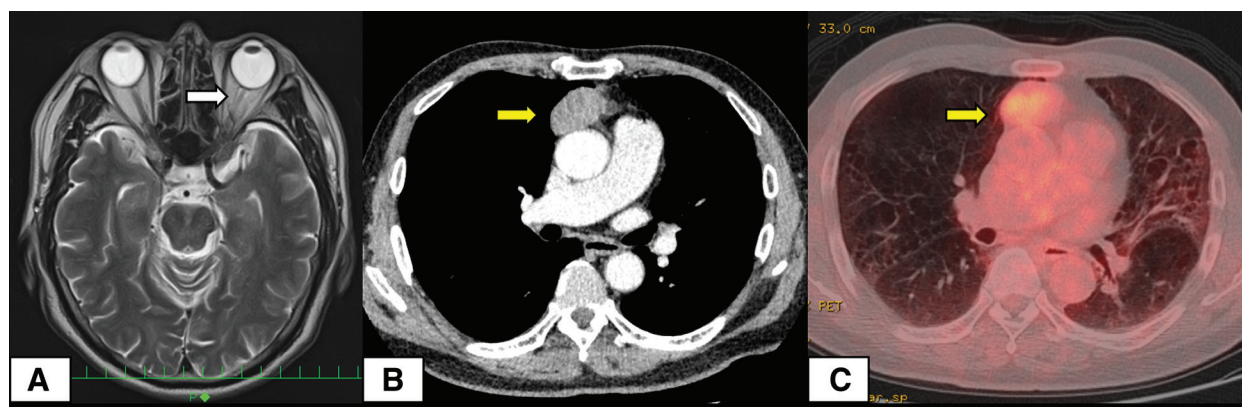
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Corresponding author: Yugo Tanaka, MD, PhD. Division of Thoracic Surgery, Kobe University Graduate School of Medicine, 7-5-2 Kusunokicho, Chuou-ku, Kobe, Hyogo 650-0017, Japan. Email: tanakay@med.kobe-u.ac.jp



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**Fig. 1** Brain MRI revealed abnormal T2-weighted hyperintensity of the left optic nerve (arrowhead, **A**). Enhanced chest CT showed an enhanced anterior mediastinal tumor, 20 × 18 mm in size (arrowhead, **B**). PET with fluorodeoxyglucose showed abnormal uptake in the anterior mediastinal tumor with a maximal standardized uptake value of 3.8 (arrowhead, **C**). CT: computed tomography; MRI: magnetic resonance imaging; PET: positron emission tomography

lobe, and left optic nerve (**Fig. 1A**). Enzyme-linked immunosorbent assay (SRL, Inc., Tokyo, Japan) for serum aquaporin-4 autoantibodies was positive (3.8 U/mL; normal range, <3.0 U/mL). The patient was diagnosed as NMOSD, and treated with three courses of high-dose intravenous methylprednisolone (100 mg/day for 3 days). This was followed by oral prednisolone, initiated at 30 mg/day and tapered to a maintenance dosage of 10 mg/day as his symptoms improved.

One year after onset of symptoms, an anterior mediastinal tumor was incidentally found on chest computed tomography (CT) scan. Contrast enhanced CT scan and MRI revealed a tumor (20 × 18 mm) in the anterior mediastinum, which was suspected of being thymoma (**Fig. 1B**). On positron emission tomography (PET), the standardized uptake value was 3.8 (**Fig. 1C**). We performed thymothymectomy through a median sternotomy. During the operation, the tumor was found to be encapsulated and not adherent to the lung. The resected specimen was a grayish-white mass (17 × 15 mm) with bleeding. The pathological study revealed mainly a nested pattern, including focal necrosis and 5 to 6 mitotic figures per 10 high-powered fields (**Fig. 2A** and **2B**). Immunohistochemical staining revealed atypical cells that expressed synaptophysin and chromogranin A. The diagnosis was atypical thymic carcinoid, Masaoka stage II. Immunohistochemistry of formalin-fixed paraffin-embedded sections revealed that the tumor cells were positive for aquaporin-4 (**Fig. 2C** and **2D**).

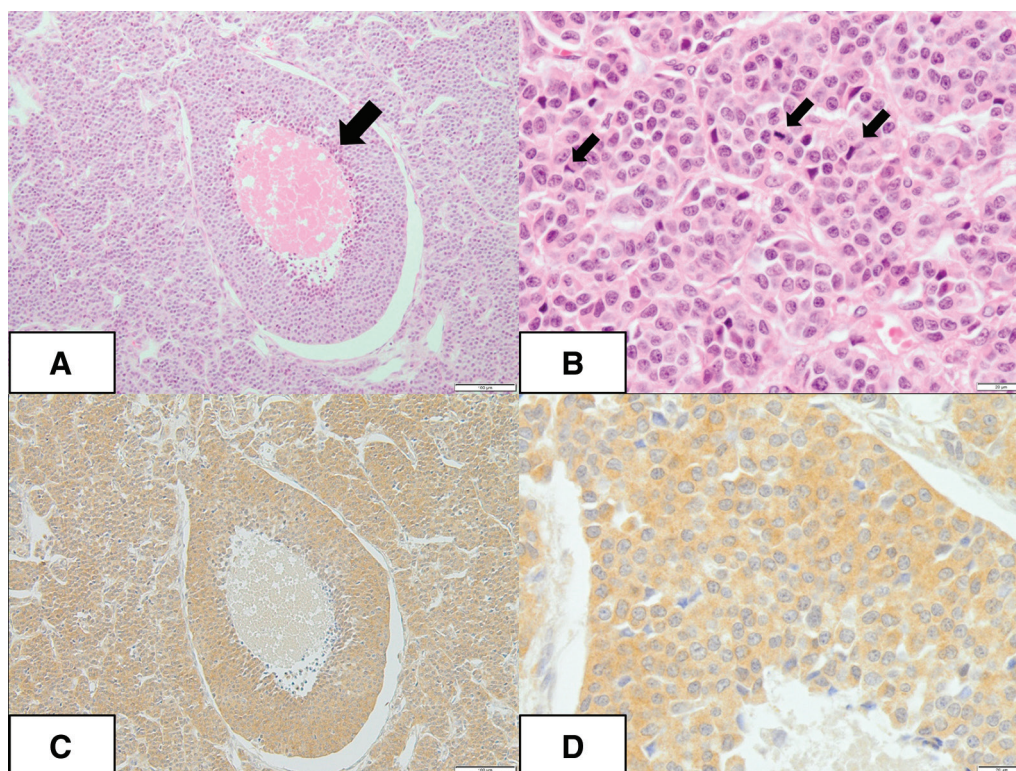
The postoperative course was uneventful. Postoperative serum aquaporin-4 autoantibodies turned negative, and follow-up MRI showed significant regression of the

optic nerve lesion after surgery. Considering the recurrence of neurologic symptoms, the patient received a continuous course of prednisolone (5 mg/day) and remained free of recurrence and symptoms 1 year after surgery.

## Discussion

Paraneoplastic neurological syndromes are caused by immune responses initiated by antineuronal antibodies expressed in cancer. These syndromes are known as remote effects of cancer that are not caused by direct invasion, metastasis, coagulation, infection, ischemia, or metabolic disruptions or by side effects of chemotherapy or radiotherapy.<sup>3)</sup> In patients with paraneoplastic NMOSD, aquaporin-4 antibodies reportedly have a direct pathogenic role in causing paraneoplastic neurological syndromes.<sup>4)</sup> NMOSD is associated with several types of malignancies such as thymoma, lung cancer, uterine or cervical cancer, breast cancer, and thyroid cancer. Aquaporin-4 autoantibody expression by tumor cells has not been extensively reported in cases of paraneoplastic NMOSD.

Distinguishing between paraneoplastic and idiopathic NMOSD is difficult but important for disease management; immunosuppressive therapy is the mainstay of treatment in idiopathic NMOSD, but there is no guidance regarding paraneoplastic NMOSD. However, some researchers have evaluated cancer-directed treatments, including surgical resection, that are useful for stabilizing the disease or ameliorating symptoms in patients with paraneoplastic neurological syndromes.<sup>5)</sup> In our patient, postoperative serum aquaporin-4 autoantibodies



**Fig. 2** Pathological examination revealed mainly a nested pattern, including focal necrosis (arrow, **A**) and 5 to 6 mitotic figures per 10 high-power fields (arrows, **B**). Hematoxylin–eosin staining (**A**, **B**). Immunohistochemical staining was positive for aquaporin-4 (**C**, **D**). Scale bars: 100  $\mu$ m (**A**, **C**) and 20  $\mu$ m (**B**, **D**).

turned negative, and he has remained free of symptoms since surgical resection. In several cases, researchers have noted that cancer-directed treatment in addition to immunotherapy improved symptoms in patients with paraneoplastic NMOSD, as in our patient. Al-Harbi et al.<sup>6</sup> reported a case of paraneoplastic NMOSD associated with stomach carcinoid tumor that was successfully treated with gastric ablation. In addition, Kon et al.<sup>7</sup> reported a case of paraneoplastic NMOSD associated with esophageal cancer that was cured by chemoradiotherapy. To elucidate clinical benefits of surgical treatment against paraneoplastic NMOSD, more detailed clinical information is needed. Surgical resection can ameliorate symptoms, and is therefore one of the most important treatments for paraneoplastic NMOSD. It is noteworthy that in our patient, neurological symptoms improved after surgical resection of the tumor-expressing aquaporin-4 autoantibodies. Moreover, immunohistochemical staining showed that aquaporin-4 autoantibodies were expressed in tumor cells but not in adjacent mediastinal fat cells, that is, sufficient improvement in neurological symptoms can be expected only after removal of the tumor.

According to a previous report, paraneoplastic NMOSD was identified in 5% of patients with aquaporin-4 seropositive NMOSD and several cancers, such as thymoma, lung cancer, breast cancer, uterine or cervical cancer, and thyroid cancer, were associated with NMOSD.<sup>2</sup> Therefore, patients with NMOSD should be examined closely for the presence of oncologic disease. In addition to CT and MRI, PET/CT appears to be useful for whole-body inspection and in detecting small tumors. Furthermore, in view of reports of stomach carcinoid and esophageal cancer in association with NMOSD,<sup>6,7</sup> gastric endoscopy appears to be useful for detecting gastrointestinal tumors.

## Conclusion

We reported a rare case of paraneoplastic NMOSD associated with thymic atypical carcinoid treated with surgical resection. This case showed the important neurological complications of thymic atypical carcinoid. Moreover, radiographic examinations on the presence of mediastinal tumors were found to be essential in patients with NMOSD.



## Disclosure Statement

None declared.

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