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Case Report

Development of Paraneoplastic Neuromyelitis Optica after Lung Resection in a Patient with Squamous Cell Carcinoma

Shunsuke Eba, MD, PhD,[1] Shuhei Nishiyama, MD, PhD,[2] Hirotsugu Notsuda, MD, PhD,[1] Hisashi Oishi, MD, PhD,[1] Masafumi Noda, MD, PhD,[1] Masashi Aoki, MD, PhD,[2] and Yoshinori Okada, MD, PhD[1]

Neurological paraneoplastic syndrome is a relatively rare condition in patients with malignant tumors. Recently, it has been reported that anti-Aquaporin 4 (AQP4) antibody is highly specific for neuromyelitis optica. The patient was a 76-year-old man. He underwent right upper lobectomy for squamous cell carcinoma of the lung. Although the immediate postoperative course was uneventful, neurological symptoms became apparent from postoperative day (POD) 4. Magnetic resonance imaging showed longitudinally extended edematous lesions in the spinal cord, and a cerebrospinal fluid examination was positive for anti-AQP4 antibody, leading to the diagnosis of paraneoplastic neuromyelitis optica. Despite multiple rounds of steroid pulse therapy and plasma exchange, the neurological symptoms worsened and the patient died on POD 46. The development of neuromyelitis optica in the early postoperative period could be related to the influence of surgical stress or epidural anesthesia.

Keywords: paraneoplastic neuromyelitis optica, lung cancer, surgical stress, epidural anesthesia

Introduction

Paraneoplastic neurological syndrome is a relatively rare condition in patients with malignant tumors. In many cases, the onset of neurological symptoms precedes the tumor detection and treatment. We report here an extremely rare case of paraneoplastic neuromyelitis optica spectrum disorders (NMOSD), which developed in the early postoperative period after lung resection for squamous cell carcinoma.

Case Presentation

A 76-year-old man was referred to our hospital for investigation of a mass on chest computed tomography (CT). His smoking history was 57 pack-years. Chest CT showed a mass 50 mm in diameter in the right upper lobe (**Fig. 1A**). The right hilar lymph nodes were enlarged to 15 mm in diameter and metastasis was suspected (**Fig. 1B**). Whole-body fluorine-18-flurodeoxyglucose positron emission tomography and CT scan showed uptakes in the mass and the right hilar lymph nodes with standard uptake value max of 16 and 4.7, respectively. No distant metastasis was observed. Brain metastasis was not indicated by magnetic resonance imaging (MRI). Sputum cytology showed squamous cell carcinoma, and bronchoscopic examination was omitted. Clinical stage was

[1]*Department of Thoracic Surgery, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Miyagi, Japan*
[2]*Department of Neurology, Tohoku University School of Medicine, Sendai, Miyagi, Japan*

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Corresponding author: Shunsuke Eba, MD, PhD. Department of Thoracic Surgery, Institute of Development, Aging and Cancer, Tohoku University, 4-1 Seiryomachi, Aoba-ku, Sendai, Miyagi 980-8575, Japan
Email: shunsuke.eba.e1@tohoku.ac.jp

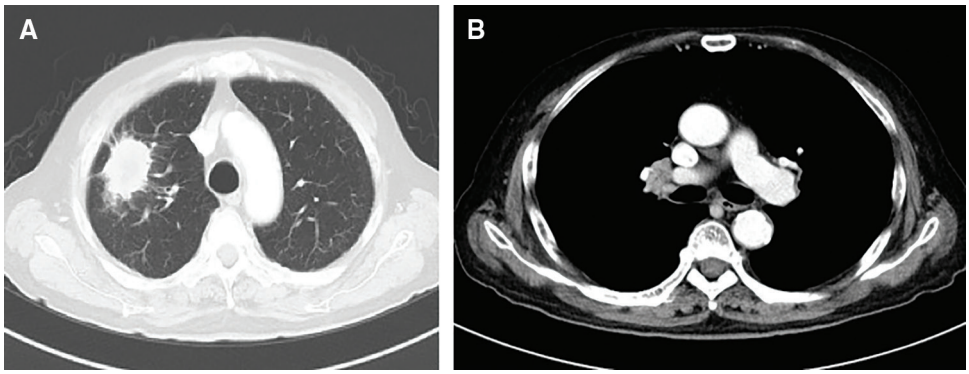

Fig. 1 Chest CT showing a 50-mm tumor in the upper lobe of the right lung (**A**) and swollen lymph node in the hilar region of the lung (**B**). CT: computed tomography

judged to be cT2aN1M0 (cStage IIb), and right upper lobectomy with mediastinal lymph node dissection was planned. Blood tests showed no particular abnormality except for the elevation of hemoglobin A1c of 8.0%. Tumor markers were elevated to squamous cell carcinoma-related antigen of 3.6 ng/mL and cytokeratin-19 fragment of 2.4 ng/mL. His Glasgow Coma Scale was E4V5M6 with no evidence of neurodegeneration, no motor or sensory deficits, and no peripheral neuropathy due to diabetes mellitus.

The video-assisted thoracoscopic surgery was performed as planned. The pathological examination of the resected specimens showed squamous cell carcinoma with a pathological stage of T2aN0M0 (pStage B). For postoperative analgesia, the administration of levobupivacaine and fentanyl via the epidural catheter was started immediately before surgery and confirmed until postoperative day (POD) 2. The patient's immediate postoperative course was uneventful. The thoracic drain was removed on POD 2 and the patient started walking on that day. On POD 4, symptoms of constipation appeared. On POD 6, he complained of weakness and numbness of the lower limbs and urinary retention. Neurological examination by a neurologist revealed bilateral sensory deficits below the first level of the thoracic spinal cord, flaccid paraparesis, hyporeflexia in bilateral lower limbs, dysuria, and bilateral Babinski's sign. We first suspected spinal cord metastasis and an urgent MRI examination was performed, which demonstrated a T2WI-high longitudinally extended angioedematous lesion in the central part of the spinal cord from below C6 to the cauda equina (**Fig. 2**). Neuromyelitis optica was suspected and a cerebrospinal fluid examination was performed on POD 8, which showed pleocytosis (113 cells/μL), an elevated protein concentration (145 mg/dL), and no oligoclonal IgG bands. With the clinical diagnosis, 1000 mg of intravenous methylprednisolone was administered for 3 days. Despite the treatment, sensory and motor disorders spread to the upper extremities on POD 12. On POD 13, the result of the spinal fluid examination revealed the presence of anti-Aquaporin 4 (AQP4) antibody the measurement method reported previously,[1] and the diagnosis of neuromyelitis optica was confirmed. Although repeated plasma exchange and another steroid pulse therapy were performed, his neurological symptoms gradually worsened, and MRI on POD 33 showed the extension of the angioedematous lesion to the brainstem. The patient died on POD 46.

Discussion

AQP4 is a protein expressed on astrocytes, a type of glial cell in the brain, and is involved in the movement of water molecules.[2] In 2004, a collaborative study between the Mayo Clinic and Tohoku University showed that patients with neuromyelitis optica had a high serum prevalence of anti-AQP4 antibodies and that anti-AQP4 antibodies target AQP4 on astrocytes in the optic nerve and spinal cord causing damage.[3] As a result, the nerves and myelin sheaths are secondarily damaged, and many degenerated mitochondria accumulate in the nerve axons, eventually resulting in axonal enlargement and degeneration.[4]

In general, neuromyelitis optica has the following clinical features: 1) the average age of onset is in the 30 to 40 s, 2) the proportion of females is extremely high (90%), and 3) MRI shows foci extending from the central gray matter to the periphery over three vertebral body lengths in the cervical and thoracic spinal cord. When neuromyelitis optica develops in elderly men, as in this case,

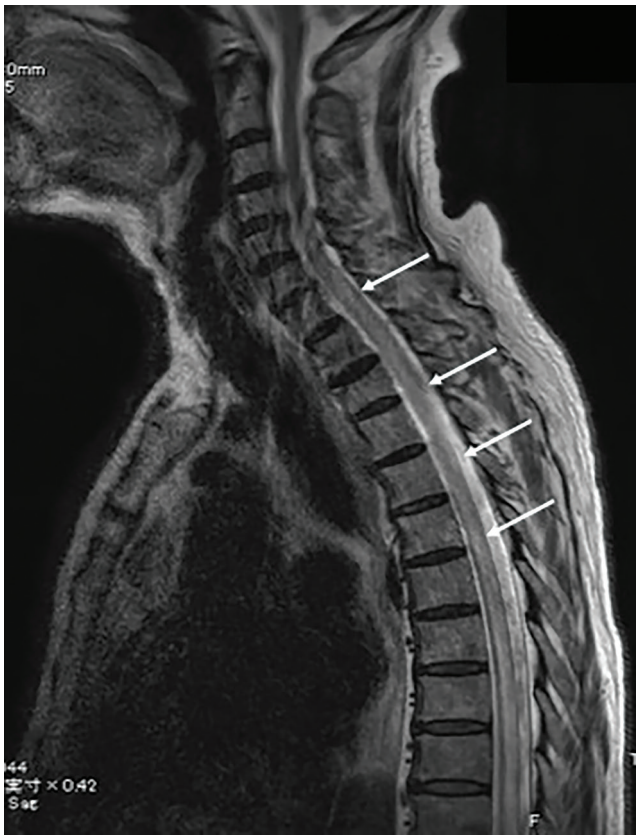

Fig. 2 Chest MRI showing a widespread T2WI- high angioedematous lesion, mainly in the center of the spinal cord. MRI: magnetic resonance imaging

paraneoplastic syndrome should be suspected and a search for malignant disease should be made.[5)]

Cases of paraneoplastic neuromyelitis optica associated with lung cancer have rarely been reported. To the best of our knowledge, there have been 8 previous reports of paraneoplastic neuromyelitis optica associated with lung cancer, including 7 cases in which the onset of neurological symptoms preceded the diagnosis of lung cancer. Unlike the cases in the previous reports, the present case first showed neurological symptoms after surgery for lung cancer. Paraneoplastic syndromes are generally identified pre or post tumor and generally improve postoperatively. However, according to a single-center cohort study of neuromyelitis optica, the time lag between the onset of neuromyelitis optica and tumor identification varies from case to case.[6)] This report includes cases of recurrence or preventive treatment even after resection of the causative tumor. According to this, paraneoplastic neuromyelitis optica, like our case, may not always improve postoperatively. Neuromyelitis optica is known to be exacerbated by fatigue, stress, and infections, which is probably associated with some alterations in the immune system in response to such stresses. In this context, surgical stress could have affected the onset of neuromyelitis optica in this case, as sometimes seen with other autoimmune diseases such as myasthenia gravis. Another possibility is that spinal and epidural anesthesia triggered the onset, as reported by Kitazaki et al. concerning bupivacaine use.[7)] Bupivacaine is known to decrease the mitochondrial membrane function and impair the glutamate clearance function of astrocytes,[8)] which are responsible for glutamate clearance from the synaptic cleft to prevent the increase in excitotoxicity caused by glutamate. In the present case, levobupivacaine was administered through an epidural catheter from the start of surgery until the second POD. With a similar mechanism, this may have triggered the clinical manifestation of the syndrome in combination with the preexisting anti-AQP4 antibody.

Conclusion

We experienced an extremely rare case of anti-AQP4 antibody-positive paraneoplastic neuromyelitis optica that developed early after resection of squamous cell lung cancer and worsened rapidly. The development of neuromyelitis optica in the early postoperative period could be related to the influence of surgical stress or epidural anesthesia.

Disclosure Statement

The authors declare that there are no conflicts of interests.

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