CASE REPORT

Paraneoplastic Neurological Syndrome in a Patient with Squamous Cell Lung Cancer

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Abstract

A 78-year-old man presented with urinary retention and difficulty walking. Both legs showed muscle weakness, and he was experiencing lower body hypoesthesia. T2-weighted magnetic resonance imaging revealed lesions with high signal intensity and enhancement in the spinal cord and cerebrum. A cerebrospinal fluid specimen showed inflammatory changes, but negative cytology findings. Chest computed tomography revealed a tumor measuring 40 mm in diameter, and a lung biopsy revealed the presence of squamous cell carcinoma. We diagnosed the patient with paraneoplastic neurological syndrome related to lung cancer. The patient was treated with steroid pulse therapy and chemotherapy, which relieved the symptoms and enabled the patient to achieve an independent gait.

Key words: paraneoplastic neurological syndrome, encephalomyelitis, lung cancer, squamous cell carcinoma, myelitis

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Introduction

Paraneoplastic neurological syndromes (PNS) are the remote effects of cancer on the nervous system that are not caused by either an invasion of the tumor or its metastases (1). The etiology of PNS is thought to be an autoimmune response resulting from the immune cross-reactivity between the tumor cells and the components of the nervous system (2, 3). In contrast to endocrine and dermatologic syndromes, which are frequently-occurring squamous cell carcinoma-related paraneoplastic syndromes (4), the overall frequency of malignancy-related PNS is reportedly only around 1%. However, PNS are seen somewhat more frequently in small cell lung cancers (SCLC), occurring in about 3% of the total cases. In addition, Graus et al. reported that out of 200 patients with anti-Hu-associated paraneoplastic encephalomyelitis (PEM), 74% had SCLC (5). Additionally, Candler et al. reported that 30% of PNS cases were associated with SCLC, while only 8% were associated with non-small cell lung cancers (NSCLC). The pathological manifestations described in these reports have yet to be elucidated (6). We herein report a rare PNS case related to squamous cell lung cancer.

Case Report

In July 2012, a 78-year-old man was referred to our hospital with acute urinary retention. A few days later, he experienced difficulty walking, which worsened during the following week and eventually resulted in abasia. The patient had a history of gastric ulcers. He did not have a history of neurological disorders, yet he exhibited muscle weakness in both legs, sensory losses to pain and temperature in the body regions below Th10 and a disturbance of deep sensibility. There was no exaggeration of deep tendon reflexes, but there was fecal incontinence and flaccid bladder. Chest computed tomography (CT) revealed a tumor of 40 mm in diameter.
Figure 1. (a) Post-gadolinium spinal cord magnetic resonance imaging (MRI) revealed high intensity lesions in the central portion of the spinal cord at Th12 as well as enhancement along the cauda equina. The lesion at the back of the vertebral body at L3 was considered bone metastasis. (b) Post-gadolinium spinal cord MRI after two cycles of steroid pulse therapy showed the significant resolution of the high intensity lesions.

diameter with a cavity in the right upper lobe (S2). The patient was admitted to our hospital for an investigation of a spinal cord injury as well as to be treated for the lung tumor.

T2-weighted magnetic resonance imaging (MRI) of the spinal cord revealed high intensity lesions in the central portion of the spinal cord at Th12 and enhancement along the cauda equina (Fig. 1a). MRI also showed an L3 lesion that was suspected of being bone metastasis. Brain MRI revealed multiple patchy areas of high signal intensity on T2-weighted, FLAIR images and diffusion-weighted images of the right occipital lobe, the frontal lobe, the bilateral temporal lobe and the periventricular white matter (Fig. 2a, b). Some of these lesions were enhanced on post-gadolinium T1 images. Brain MR angiography was normal. An analysis of the cerebrospinal fluid (CSF) showed elevated levels of protein as well as pleocytosis, but negative cytology (Table). The nerve conduction velocities in both the median and posterior tibial nerves were within normal limits. Upon laboratory examination, the patient was found to have elevated levels of the following analytes: lactate dehydrogenase (663 IU/L), C-reactive protein (0.6 mg/dL), carcinoembryonic antigen (7.6 ng/mL), cytokeratin 19 fragment (4.0 ng/mL) and anti-cyclic citrullinated peptide antibody (62.2 U/mL). The angiotensin converting enzyme (ACE) test was within the normal limit (21.2 IU/L), and all of the other tests for antibodies related to collagen diseases, including anti SS-A/B, were negative. The dot blot analyses of the serum were negative for anti-Hu, anti-Yo, anti-Ri, anti-CV2, anti-Tr, anti-Ma-2 and anti-amphiphysin.

Although no anti-neuronal antibody was found, the presence of a classical myelitis-related syndrome, the patient’s age and lack of prior neurological disease history and the co-existence of lung cancer led to a definitive diagnosis of PNS based on the PNS diagnostic criteria (7). The patient was administered 1,000 mg of methylprednisolone (mPSL) for 3 consecutive days with the expectation that the anti-inflammatory effects would relieve the myelitis. This treatment was followed with 15-20 mg of prednisolone daily. With the therapy, the muscle strength in the patient’s lower extremities improved his ability to demonstrate a crouch gait, and the area of sensory loss gradually diminished until it was only localized to the right lower extremity. A bronchial lung biopsy showed moderately differentiated squamous cell carcinoma with partial cornification. The clinical staging was T2aN0M1b (bone), stage IV. In order to treat the residual sensory loss and the fecal incontinence, we administered a second mPSL pulse 3 weeks later, but this treatment was terminated because the patient developed an enteral infection.

Follow-up MRI after two cycles of steroid pulse therapy showed significant resolution of the spinal cord and cerebral hyperintensities (Fig. 1b, 2c, d). Because the patient was in good general condition, he was administered 4 cycles of chemotherapy including the administration of carboplatin plus gemcitabine on day 1 and day 8. The antitumor response was stable disease. A follow-up CSF analysis was not performed. Although the sphincter dysfunction and the sensory loss in a portion of the right sole persisted, his neurological symptoms stabilized during the chemotherapy and remained stable thereafter.
In the majority of cases, patients exhibiting PNS have SCLC (5, 8) complicated by PEM, which is often associated with a sensory neuropathy. PEM manifests as several different clinicopathological entities and often involves multifocal syndromes such as paraneoplastic limbic encephalitis (PLE), myelitis and peripheral neuropathy (7, 9). In the present case, the patient was found to have flaccid paralysis of the lower limbs bilaterally, fecal incontinence and segmental sensory loss. These findings suggested myelopathy. The differential diagnosis included a metastatic spinal cord tumor, vascular disease, neurosarcoidosis and collagen-related myelitis. Regarding brain MRI, the differential diagnosis included multiple sclerosis, neuromyelitis optica, a metastatic brain tumor and cerebrovascular disease. In our case, the negative results for the CSF cytological analysis combined with the absence of any meningeal enhancement or mass effect on MRI helped to exclude leptomeningeal and cerebral metastases. Furthermore, CSF pleocytosis was seen, even though neither oligoclonal bands nor myelin basic proteins were detected. None of the physical findings suggested collagen disease, and neuromyelitis optica was excluded based on the absence of optic nerve lesions. In addition, we noted an absence of any ACE elevation, mediastinal lymph node swelling and uveitis, which would have indicated sarcoidosis. The pathological findings also did not support sarcoidosis.

The detection of neuro-antibodies could suggest an autoimmune etiology, but 16-25% of SCLC patients express anti-Hu antibodies without any neurological disturbance (10). Moreover, the titers of these antibodies were unaffected by treatment, suggesting that autoantibodies do not act alone in causing PNS. In addition, regulatory T-cell dysfunction appears to contribute to the collapse of self-tolerance and PNS development (11). Although the frequency of autoantibody production in patients with NSCLC is as yet unknown, Candler et al. reported 5 NSCLC pa-
Patients complicated by PNS, all of whom expressed antineuronal antibodies (3 anti-Hu, 1 anti-Yo, 1 anti-Misc) (6). In a review of 50 PLE patients who either did not express antibodies or who exhibited atypical antibodies, 5 had NSCLC. Of those, at least one patient had anti-Hu (12).

In our case, the patient’s lung cancer and antecedent neurological symptoms met the clinical criteria for PNS. Moreover, steroid pulse therapy and chemotherapy stabilized the neurological syndrome and resolved the MRI abnormalities. Gultekin et al. reported that 28 (64%) of 44 PLE patients had abnormal MRI findings, such as unilateral or bilateral temporal lobe abnormalities on T2-weighted images, and 5 (20%) of 25 patients had enhanced lesions (12). In addition, in most cases of PLE, 18F-FDG PET usually shows hypermetabolism in the temporal lobes with negative findings on MRI or the presence of T2-hyperintense mesiotemporal lesions, and the 18F-FDG PET may be correlated with disease activity (13).

Based on the patient’s age, the absence of a prior neurological disease history, the MRI findings and the coexistence of lung cancer, we concluded that the most likely diagnosis was PNS (PEM), even though multiple sclerosis could not be definitely excluded. Steroid pulse therapy was administered with the aim of reducing the spinal cord edema and relieving the neural symptoms that were caused by the myelitis. The early detection of PNS and the treatment of the tumor(s) have a reportedly greater impact on the neurological outcome (14, 15) than the use of immunosuppressive therapies (16). The clinical course of this patient was highly consistent with the diagnosis of PNS. The frequency of PNS accompanying squamous cell carcinoma is rare, but, given the association between an early treatment and favorable outcomes, it should be considered in the differential diagnosis in cases of acute widespread neurologic deterioration.

The authors state that they have no Conflict of Interest (COI).

References