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Case report

Anti-NMDAR encephalitis in small-cell lung cancer: A case report

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1. Introduction

Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune encephalitis involving anti-NMDAR antibodies, which are specific to the NR1/NR2 heteromers of the NMDAR [1]. Previous reports have described the following clinical features in association with anti-NMDAR encephalitis: occurrence mostly in young women, schizophrenia-like psychiatric symptoms, seizures, an unresponsive/catatonic state, central hypoventilation, orofacial-limb dyskinesias, decreased level of consciousness, and autonomic symptoms [1–3]. About 53% of patients with anti-NMDAR encephalitis older than 18 years had tumors, most commonly ovarian teratomas, though the detection of an underlying tumor is dependent on age, sex, and ethnic background [3]. While rare, the following tumors were reported as underlying ones: testicular germ-cell tumor, Hodgkin lymphoma, neuroendocrine tumor of the ovary, sex cord stromal tumor of the ovary, pseudopapillary neoplasm of the pancreas, breast cancer, neuroblastoma, and small-cell lung cancer (SCLC) [2,3]. Dalmau et al. mentioned a 76-year-old male with anti-NMDAR encephalitis with SCLC, but detailed information was not provided [2]. In this report, we describe a 68-year-old male presenting with anti-NMDAR encephalitis in SCLC.

2. Case report

A 68-year-old man presented to a psychiatric service with a week-long history of emotional and behavioral changes. His past medical history was unremarkable, except for a flu-like illness 2 weeks before symptom onset. According to the medical history obtained from his family members, his baseline mental functioning was supposed to be normal. When he came to the psychiatric service, he had delusions, hallucinations, and emotional incontinence, and was diagnosed as senile psychosis. However, the psychiatric symptoms were aggravated over the following few days, and he was admitted to neurological intensive care unit in our hospital for suspected organic psychosis. Upon admission, his level of consciousness was impaired (Glasgow Coma Scale (GCS) score of 11). The patient showed confusion, agitation, and aggression. There were no meningeal signs, and his reflexes were normal, without extensor plantar responses. Signs of respiratory illness and cachexia were not observed at this time.

Routine laboratory studies showed normal findings with a slightly elevated titer of C-reactive protein. The test for antinuclear antibodies was negative. Cerebrospinal fluid (CSF) analysis showed lymphocytic pleocytosis (29/mm^3) with normal protein and glucose concentrations. Cytological examination of the CSF showed no malignant cells. CSF cultures were negative for bacteria, fungi, and mycobacteria, and polymerase chain reaction to test for herpes simplex virus (HSV PCR) was negative. A markedly elevated pro-gastrin-releasing peptide titer (796 pg/ml; normal range, less than 46 pg/ml) was found in the serum, although other tumor markers including neuron-specific enolase, CEA, CA19-9, SCC, and cytokeratin fragment 21-1 were all negative. Brain magnetic

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resonance imaging findings were unremarkable on T1-weighted images, T2-weighted images, fluid-attenuated inversion recovery images, diffusion-weighted images, and post-contrast T1-weighted images. There were no metastatic deposits on brain magnetic resonance imaging. Single photon emission computed tomography of the brain using ^{99m}Tc-ECD showed slight hypoperfusion in the bilateral frontal and parietal lobes. Electroencephalogram showed diffuse delta waves without epileptic discharges. Nerve conduction studies were normal in the bilateral median, ulnar, tibial, and sural nerves. Computed tomography of the chest and abdomen revealed a 3.3 cm × 2.2 cm tumor in the right S6 segment of the lung, with satellite nodules within the same lobe, visceral pleural invasion, and ipsilateral hilar and subcarinal lymph node metastasis. The tumor-node-metastasis classification was T3N2M0, stage IIIA. Serum paraneoplastic antibodies including anti-Hu, anti-Yo, anti-Ri, anti-CV2 (CRMP-5), anti-Tr, anti-Ma2, and anti-amphiphysin were all negative. CSF obtained on day 1 was tested for antibodies to NMDAR with a method described previously [1]: screening for antibodies that react with HEK cells transfected to express NR1 and NR2 subunits of NMDAR. Anti-NMDAR antibodies were identified in the CSF (the patient's serum sample was not tested). Cytology by transbronchial lung curettage was performed by pulmonologists, revealing a SCLC.

Initial treatment with acyclovir (1500 mg/day), meropenem (6 g/day) and high-dose intravenous methylprednisolone (IVMP) (1000 mg/day for 3 days) was started. Acyclovir and meropenem were used until the negative results of HSV PCR and CSF culture were obtained. In addition, sedation with continuous intravenous infusion of propofol was started against his agitated and aggressive behaviors. Chemotherapy for SCLC was not performed because his family requested conservative care only. When sedation was discontinued on day 7, he was unresponsive to verbal commands although his eyes were open (GCS score of 9). The patient started an additional course of high-dose IVMP. Beginning on day 8, oral dyskinesia including masticatory movement was observed intermittently. Rhythmic movements in his upper extremities, such as playing the piano, were also seen occasionally. These involuntary movements disappeared gradually over the following five to six weeks. Anticonvulsants did not seem to be effective in treating them. On day 15, he demonstrated central hypoventilation, and he was intubated and mechanically ventilated for a month. Autonomic dysfunction such as abnormal blood pressure variability and sudoresis were occasionally observed during this time period. A sleep disorder characterized by alternating insomnia and hypersomnia was observed around two to five months after his admission. Although his intellectual function was disrupted, his consciousness level was almost normal around five months after admission (GCS score of 14). Meanwhile, SCLC had progressed, and cancer cachexia had developed. On day 188, the patient died of respiratory failure. Autopsy was not performed.

3. Discussion

The present patient presented with psychiatric symptoms that were preceded by flu-like symptoms and followed by disturbance of consciousness, involuntary movements, central hypoventilation, and autonomic symptoms. Except for lack of seizures, these symptoms share clinical features of anti-NMDAR encephalitis previously reported [1–3]. We detected anti-NMDAR antibodies in the patient's CSF and diagnosed as anti-NMDAR encephalitis.

Onconeural antibodies such as anti-Hu, anti-CV2, and anti-amphiphysin, and anti-$GABA_B$ receptor antibody, one of the antibodies against neurosurface antigens, are known to be associated with SCLC [4]. On the other hand, the association of anti-NMDAR antibodies with SCLC has been hardly reported. Unfortunately, we could not clarify whether the SCLC tissue in our case expressed cross-reactive antigens with anti-NMDAR antibodies because we could not obtain the tumor tissue. However, North et al. showed that SCLC tissues and lines of cells derived from SCLC tumors expressed NMDAR [5]. This finding suggests that SCLC could plausibly trigger the production of anti-NMDAR antibodies.

It should be noted that the patient did not present clinically with SCLC before admission. In paraneoplastic limbic encephalitis, psychiatric disturbance can precede diagnosis of underlying tumors by over a year. Periodic screening for tumors for at least 2 years is recommended in anti-NMDAR encephalitis, even if patients have recovered from encephalitis [3].

There has been no sufficient evidence of treatment options for anti-NMDAR encephalitis yet, but most recently Dalmau et al. reviewed more than 400 patients with anti-NMDAR encephalitis and proposed a therapeutic strategy [3]. In the proposed strategy, pulsed methylprednisolone plus intravenous immunoglobulin or plasma exchange is recommended as first-line therapy. If no response is seen after 10 days, they suggest rituximab, cyclophosphamide or both as second-line therapy. In patients with tumors, such immunotherapies in conjunction with tumor removal are emphasized. Indeed, treatment of underlying tumors is not always possible when they are very malignant as in our case, but it should be taken into consideration.

4. Conclusion

We report the case of a patient with anti-NMDAR encephalitis in SCLC. When patients with SCLC present with neurological manifestations, measurement of anti-NMDAR antibodies should be considered in addition to other paraneoplastic antibodies such as anti-Hu.

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