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LETTER TO THE EDITOR

Anti-*N*-methyl-D-aspartate receptor encephalitis with lung adenocarcinoma

Ying-Ying Wu[1] · Xian-Jun He[2] · Mi-Lan Zhang[1] · Ying-Ying Shi[1] · Jie-Wen Zhang[1]

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Dear Editor,

Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis was first described in 2007 as autoimmune encephalitis involving anti-NMDAR antibodies that specifically recognize NR1/NR2 heteromers of the NMDAR. The characteristics of anti-NMDAR encephalitis include schizophrenia-like psychiatric and autonomic symptoms, seizures, central hypoventilation, orofacial-limb dyskinesias, an unresponsive/catatonic state, and a decreased level of consciousness [1, 2]. In the initial report, all patients with anti-NMDAR encephalitis were women; approximately 59 % of the patients had tumors, most commonly ovarian teratomas [1]. The following tumors are rare but reported underlying diseases of anti-NMDAR encephalitis: 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) [1, 2]. We present a case of anti-NMDAR encephalitis with lung cancer (Fig. 1).

A 60-year-old man presented to a local hospital with sudden onset of weakness in the left limbs at five o'clock in the morning, on July 13, 2014. He had a history of hypertension and smoking. Head computed tomography (CT) showed normal findings. Brain magnetic resonance imaging (MRI) revealed multiple acute infarctions in the bilateral cerebral and cerebellar hemispheres. Magnetic resonance angiography (MRA) revealed segmental stenosis of the A1 segment of the right anterior cerebral artery. On the morning of July 18, the patient was found unresponsive, with decorticate rigidity and urinary incontinence. MRI revealed acute infarction in the left cerebral peduncle, basal ganglia region, periventricular area, both centrum semiovale, and splenium of the corpus callosum (Fig.1). Enhanced MRI also revealed meningeal thickening and enhancement. MRA revealed left middle cerebral artery occlusion. Blood tumor markers indicated elevated levels of neuron-specific enolase (55.64 ng/mL), carcinogen-embryonic antigen (5.67 ng/mL), carbohydrate antigen 199 (48.13 ng/mL), carbohydrate antigen 125 (645.3 U/mL), carbohydrate antigen 724 (7.29 U/mL), and non-SCLC antigen 211 (11.26 ng/mL). CT of the chest and midsection revealed (1) a 27.8 × 25.6-mm tumor in the middle lobe of the right lung (Fig.1); (2) enlarged lymph nodes in the bilateral neck, left armpit, bilateral mediastinum, and retroperitoneal region; (3) fibrous stripes on the left apex of the lung; and (4) pleural effusion on the left side. The tumor-node-metastasis classification of the tumor was T4 N3 M_X, stage IV. The living tissue resected from the left neck mass using needle puncture biopsy was suggestive of cervical lymph node metastases and adenocarcinoma. The patient received targeted drug therapy with icotinib hydrochloride tablets (Conmana).

The patient was transferred to our department of neurology on August 11. Physical examination results showed mental confusion, unresponsiveness to stimulation, and decorticate rigidity. The patient had hyperactive tendon reflexes and Babinski sign was present bilaterally. Owing to his condition, he could not undergo additional physical examinations. The test results for antinuclear and antithyroid antibodies were negative. Evaluation of the cerebrospinal fluid (CSF) sample showed normal intracranial

✉ Jie-Wen Zhang
zhangjiewen9900@126.com

[1] Department of Neurology, Zhengzhou University People's Hospital, Zhengzhou 450003, Henan, China

[2] Department of Neurology, First People's Hospital of Shangqiu City, Shangqiu, China

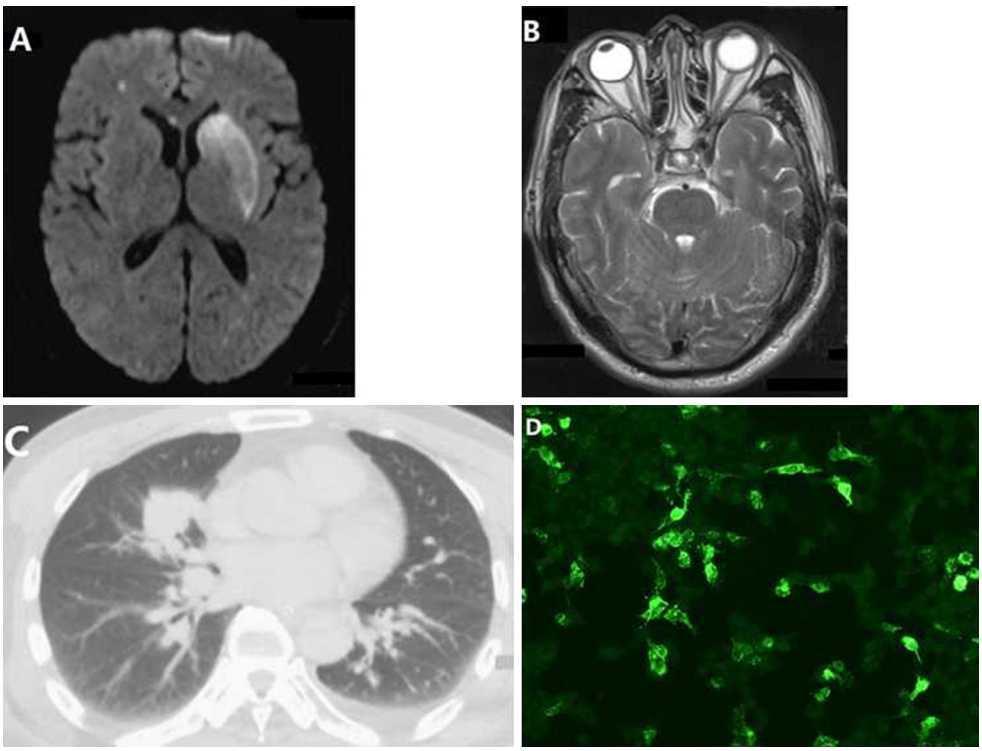

Fig. 1 **a** DWI lesion of the patient. It showed hyperintensity in basal ganglia. **b** T2 weighted images of the patient. It showed normal sign in limbic system. **c** Chest CT of the patient. It showed a mass in the middle lobe of right lung. **d** CSF anti-NMDAR antibodies transfected cells image. *DWI* diffusion-weighted image, *CSF* cerebral spinal fluid, *NMDAR N*-methyl-D-aspartate

pressure (150 mmH_2O), 23 leukocytes, an elevated glucose level (4.68 mmol/L), a normal protein level (0.30 g/L), and a normal chlorine level (120 mmol/L). The results of the viral serological and CSF analyses (*Mycoplasma pneumoniae*, herpes simplex viruses, Epstein-Barr virus, cytomegalovirus, rubella virus, and toxoplasma) were negative. Serum was negative for NMDAR antibody, but the CSF was positive for NMDAR antibody (Fig 1). The results for other serum paraneoplastic markers, including anti-Yo, anti-Hu, anti-Ri, anti-voltage-gated calcium channel, anti-voltage-gated potassium channel, and glutamic acid decarboxylase antibody were negative. The patient then received methylprednisolone sodium succinate at 500 mg/day via intravenous infusion for 3 days, then he was responsive to stimulation; however, the decorticate rigidity persisted. On day 12, the family members of the patient requested transfer to a local hospital because of shortage of money. The 1-month follow-up via telephone revealed that the decorticate rigidity was still present but the patient was able to smile at his relatives a few times. At the 6-month follow-up via telephone, the patient could make sounds but could not communicate; he experienced muscle weakness in his left limbs and he was unable to perform activities of daily living. At the 7-month follow-up, serum and CSF were negative for NMDAR antibodies.

We reported the clinical course of an elderly patient with anti-NMDAR encephalitis with lung cancer. The first presenting symptoms were neurological defects, followed by disturbance in consciousness and decorticate rigidity within 5 days. Brain MRI revealed acute infarction, perhaps related to cancer coagulopathy. These symptoms differ from those previously described for anti-NMDAR encephalitis [1, 2]. In a previous report, NMDAR antibody testing in the CSF was more sensitive compared to that in serum: NMDAR antibodies were always present in CSF, but were only detected in the serum of 86.8 % of the patients [3]. Similarly, we detected anti-NMDAR antibodies in our patient's CSF but not in the serum. However, because the CSF contained NMDAR antibodies, we diagnosed the patient with anti-NMDAR encephalitis.

This case illustrates the challenges associated with diagnosing anti-NMDAR encephalitis early in the course of the disease. Anti-NMDAR encephalitis is a syndrome with multistage development of symptoms, which include psychiatric symptoms, seizures, involuntary movements, speech disturbance, autonomic dysfunction, central hypoventilation, and insomnia. Most adult patients first present with various psychiatric symptoms or memory disorders [1], whereas pediatric patients commonly present with seizures and movement disorders. However, many

patients also have asymptomatic anti-NMDAR [4], as did our patient.

Onconeural antibodies against neuro-surface antigens such as anti-Hu, anti-CV2, anti-amphiphysin, and anti-$GABA_BR$ are closely associated with SCLC. Anti-NMDAR encephalitis with SCLC is rare, and anti-NMDAR encephalitis with lung adenocarcinoma is even more rare. North et al. [5] found NMDAR expression in SCLC tissues and cell lines derived from SCLC tumors. Unfortunately, we could not obtain a lung tumor sample from our patient. Therefore, we could not determine whether the lung tumor in our patient expressed antigens cross-reactive with anti-NMDAR antibodies or whether there is a causative relationship between lung tumors and the presence of these antibodies, despite other types of cells being present in adenocarcinomas (e.g., small cell carcinoma cells). However, our case suggests that lung cancer can trigger the production of anti-NMDAR antibodies.

It should be noted that our patient did not present clinically with lung cancer before admission. In paraneoplastic limbic encephalitis, psychiatric disorders can precede the diagnosis of underlying tumors by more than 1 year. Even if patients had recovered from encephalitis, those with anti-NMDAR encephalitis were recommended to undergo periodic screening for tumors for at least 2 years [2].

The treatment of anti-NMDAR encephalitis has not been established owing to insufficient information. However, after reviewing more than 400 patients with this disease, Dalmau et al. [2] proposed a therapeutic strategy consisting of pulsed methylprednisolone plus intravenous immunoglobulin or plasma exchange as the first-line therapy. They also recommended rituximab, cyclophosphamide, or both as the second-line therapy if a response was not achieved after 10 days. For anti-NMDAR encephalitis with tumors, immunotherapy together with tumor removal was suggested. Treatment of underlying tumors is not always possible when cancer has spread, as in our case, but it should be considered. The overall prognosis of anti-NMDAR encephalitis is favorable. About 75 % of patients with anti-NMDAR encephalitis completely recover or have only mild sequelae, whereas the rest of the patients continue to have severe disabilities or die. Nevertheless, the prognosis of anti-NMDAR is significantly better than that of other types of paraneoplastic encephalitis [1].

We report a case of anti-NMDAR encephalitis with lung adenocarcinoma. When patients with lung cancer present with neurological defects, measurement of anti-NMDAR antibodies should be considered in addition to the measurement of $GABA_BR$ antibodies or other paraneoplastic antibodies such as anti-Hu.

Compliance with ethical standards

Conflict of interest All authors have no conflict of interest to declare.

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