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Four kinds of antibody positive paraneoplastic limbic encephalitis: A rare case report

Huang P and Xu M PLE with 4 positive antibodies

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Abstract

BACKGROUND

It is not uncommon to develop autoimmune encephalitis and paraneoplastic neurological syndromes (PNS). 4 kinds of antibody-positive autoimmune paraneoplastic limbic encephalitis (PLE) have not been reported.

CASE SUMMARY

PNS are distant effects of cancer on the nervous system, rather than syndromes in which cancer directly invades and metastasizes to the nerves and/or muscle tissues. If the limbic lobe system of the brain is involved, this will result in PLE. The detection of patients with PNS is challenging since tumors that cause paraneoplastic neurologic disorders are often asymptomatic, obscure, and thus easily misdiagnosed or missed. Currently, single- or double-antibody-positive paraneoplastic marginal encephalitis has been reported. However, no cases of three or more-antibody-positive cases have been reported. Here, we report a case of PLE that is anti-collapsing response-mediator protein-5, anti-neuronal nuclear antibody-type 1, anti-aminobutyric acid B receptor, and anti-glutamate dehydrogenase positive, and address relevant literature to improve our understanding of the disease.

CONCLUSION

This article reports on the management of a case of PLE with four positive antibodies, a review of the literature, in order to raise awareness among clinicians.

Key Words: Paraneoplastic limbic encephalitis; anti-collapsing response-mediator protein-5; anti-neuronal nuclear antibody-type 1; anti-aminobutyric acid B receptor; anti-glutamate dehydrogenase; Case report

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Core Tip: This patient mainly had persistent epilepsy as the main clinical manifestation, and a lumbar puncture examination showed anti-collapsing response mediator protein-5; anti-neuronal nuclear antibody-type 1; anti-aminobutyric acid B receptor; anti-glutamate dehydrogenase positive, and further improvement of chest computed tomography and medical examination showed lung small cell carcinoma.

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INTRODUCTION

Autoimmune encephalitis (AE) refers to a class of encephalitis mediated by the autoimmune mechanism. With the continuous development of examination technology in recent years, a variety of AE-related antibodies have been found, among which anti-aminobutyric acid B receptor (GABA-BR) and anti-glutamate dehydrogenase (GAD) antibodies are most common. Rather than direct lyses and transference to nerve, muscle, or neuromuscular joints, paraneoplastic neurological syndromes (PNS) refer to the long-term effects of tumors on the nervous system. In recent years, a variety of antibodies have been found in serum or cerebrospinal fluid of PNS patients, which contribute to the diagnosis of PNS.

When AE combined with tumor, it is called parathymoma-associated AE, and if it conforms to the limbic system, it is called Paraneoplastic limbic encephalitis (PLE).

CASE PRESENTATION

Chief complaints

A 50-year-old male was hospitalized mainly because of “repeated loss of consciousness, convulsions of limbs, and abnormal mental behavior for 10 d”.

History of present illness

Ten days before his admission into the hospital, the patient suddenly fell onto the ground while working. After his fall, people tried to speak to him, but he did not reply, his teeth were clenched and his eyes turned upwards. About 2-3 min later, his

convulsions stopped and he gradually recovered consciousness. Then he complained that he felt pain and discomfort throughout his entire body, but no incontinence was present. His limb movement was disorderly and his pronunciation was unclear. He was admitted to the local hospital for treatment and his disease was considered to be "epilepsy", and thus sodium valproate was used to treat him. On the night of admission, the patient began to exhibit nonsensical behavior: he played with his fingers, kept making the beds, and was biting the quilts. At night, he was in high spirits and walked around. After treatment in the local hospital, the symptoms of loss of consciousness and limb convulsions still repeated. After performing chest computed tomography (CT) and considering lung cancer, the lung puncture examination indicated that the lower leaf of the right lung was on base section: small cell lung cancer, low-differentiated adenocarcinoma, salivating adenocarcinoma, immunohistochemistry which signaled small cell lung cancer. After the patient underwent convulsion again and did not recover consciousness, he was then urgently transferred to our hospital. The emergency department diagnosed him with "epileptic continuity". He was also diagnosed with lung cancer and admitted to our hospital.

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History of past illness

He had no special medical history.

Personal and family history

He had been smoking for 30 years with 20 cigarettes per day. He had no alcohol habits.

Physical examination

Admission check: body temperature 38.6 °C, wet rales can be heard at the base of both lungs. There were no obvious cardiac abnormalities. Nervous system check: Sleepy, Inability to cooperate with cognitive function tests. Double pupils were circular and their diameters were about 2.5 mm, but they appeared dull to light reflection. No obvious facial tongue palsy and the post-group cranial nerve was not willing to

cooperate. There was no atrophy or involuntary movement of the limbs, and the muscle tone of the limbs decreased. During pain stimulation, flexion movements of the limbs were visible. Sensory system and working movement were not willing to cooperate. No movement in the limbs and weak tendon reflexes. Negative pathological signs and signs of meningeal irritation.

Laboratory examinations

The number of blood leukocytes was $20.69 \times 10^9/L$ ($3.5-9.5 \times 10^9/L$), of which neutral cells accounted for 94% (40-75%). CRP 0.499 mg/L (0.5-10 mg/L), blood sink, serum tumor markers, clotting, acute infection-related items, liver and kidney function, electrolytes, blood lipids, and a functional, autoimmune antibody spectrum were negative.

Imaging examinations

CT revealed no abnormality in his brain essence. After scanning and strengthening the chest CT, an increase of soft tissue cluster shadows near the lower left of the right lung was visible (Figure 1A and B). The local bronchial was slightly blocked and there was a strip of increasing density shadow in the distant lung. Considering the possibility of central lung cancer, we recommended him to undergo further fiber optic examination. Scanning and strengthening the head magnetic resonance imaging (MRI) revealed that the left hippocampus was thickened, and there was a signal that fluid attenuated inversion recovery (FLAIR) was slightly higher. After the thickening of the left hippocampus, there was a strip of high signal shadow near the left hippocampus and temporal lobe. There was no dispersion restriction near diffusion-weighted imaging (Figure 2A-D).

Further diagnostic work-up

Serum paratumor-related series anti-collapsing response mediator protein-5 (CRMP5/CV2) and anti-neuronal nuclear antibody-type 1 (ANNA1/Hu) antibody were

positive. After perfecting lumbar puncture, the results indicated that the cerebrospinal fluid was colorless and transparent, pressure 260 mmH₂O (1 mmH₂O = 0.009 kPa), protein quantification 0.69 g/L (0-0.43 g/L), cerebrospinal fluid nuclear cell $0.008 \times 10^9/L$ ($0-0.015 \times 10^9/L$), adenosine deaminase: 5 U/L (0-4 U/L). Cerebrospinal fluid AE examination showed GABA-BR antibody IgG (++1:10), anti-GAD antibody IgG (+1:10). Cerebral spinal fluid nervous system paratumor syndrome series, herpes simplex virus DNA testing, TB DNA, ink staining, antacid staining were all negative. Video electroencephalography showed that before the illness, the patient's electroencephalography was in sleeping I waveform. The left forehead to the top was most significant. There were many fast waves between medium and high wave amplitude and then there was a collection-like trend spreading to the whole guide wave range and exhibiting high waves. It was mixed with ratchet rhythm and myoelectric promiscuity phase and the patient exhibited synchronized strong straight state. When the patient underwent numerous convulsions, the brain wave fully showed very high wave amplitudes until 2-3 Hz, after which a gradual slowdown appeared. This decrease to restore the background brain wave indicated that the background brain waves were mainly low, medium-wave slow wave activities. There was no obvious α wave in the top area. As for the sleep brain wave, there was no obvious K-composite wave (Figure 3). During the sleeping period, there was slow wave and rapid eye rotating.

FINAL DIAGNOSIS

The diagnoses of the patient were: (1) paraneoplastic limbic encephalitis with positive anti-CV2, anti-Hu, anti-GABA-BR, and anti-GAD; (2) secondary status epilepticus (Generalized tonic-clonic seizure); (3) right lung cancer; and (4) lung infection.

TREATMENT

The patient was given methylprednisolone and gamma-globulin shock treatment, epilepsy control, antiviral and anti-infection treatments, nutritional support, and

multidisciplinary collaboration treatment. After 17 d, his limb convulsions, nonsensical behavior, and fever symptoms were gradually controlled.

OUTCOME AND FOLLOW-UP

After the patient's admission to our hospital, our hospital provided methylprednisolone and gamma-globulin shock treatment, epilepsy control, antiviral and anti-infection treatments, nutritional support, and multidisciplinary collaboration treatment. After 17 d, his limb convulsions, nonsensical behavior, and fever symptoms were gradually controlled. When the patient was ready to be discharged from the hospital, he exhibited a slightly slow response, poor memory, and poor self-care performance. Two months later, through telephone consultation, our hospital was informed that he could eat independently and maintain brief conversations. The patient signed an informed consent document and expressed his knowledge of the study.

DISCUSSION

AE refers to a class of encephalitis mediated by the autoimmune mechanism. It was first reported by Corsellis that AE represented approximately 10%-20% of encephalitis cases^[1]. AE often affects the hippocampus, temporal lobe, and dentate gyrus, and exhibits clinical manifestations such as acute or sub-acute epilepsy-like seizures^[2], nonsensical and abnormal behavior, and memory loss. With the continuous development of examination technology in recent years, a variety of AE-related antibodies have been found, among which anti-GABA-BR and anti-GAD antibodies are most common. GABA-BR is widely expressed in the hippocampus, cortex, and cerebellum, and belongs to the inhibitory receptors of the central nervous system^[3]. When GABA-BR are knocked down in mice, convulsive behavior results, which is associated with the removal of GABA-BR inhibition in the central nervous system. GAD is a catalytic aminobutyric acid that is catalyzed in cells. As a speed limit enzyme, the GABA complex plays a role in central nervous system inhibitory dystonia and can catalyze the transformation of glutamate into the inhibitory neurotransmitter GABA.

Currently, it is believed that anti-GAD represents the connection between positive encephalitis patients and their non-tumor autoimmune diseases^[4]. Clinical manifestations mainly consist of affected temporal lobes after which epilepsy-like symptoms appear with poor prognosis.

Rather than direct lyses and transference to nerve, muscle, or neuromuscular joints, PNS refers to the long-term effects of tumors on the nervous system. In recent years, a variety of antibodies have been found in serum or cerebrospinal fluid of PNS patients, which contribute to the diagnosis of PNS. The Hu antibody, also known as ANNA1, is a multi-cloned IgG antibody. The target antigen of Hu is found in the central and peripheral nervous system of all neurons as well as in tumor cells. The anti-Hu antibody in tumor patients can attack the tumor, but will also attack the central or peripheral nervous system at the same time, which causes symptoms to appear^[5]. Studies have shown that anti-Hu antibodies exhibit a high specificity (95%-100%) and sensitivity (> 80%) to PNS diagnosis^[6]. CRMP-5 is widely expressed in the hippocampus and cortex and promotes synaptic proliferation^[7]. Furthermore, CRMP-5 can also be highly expressed in small cell lung cancer and thymus tumor and promotes tumor proliferation. CV2 antibody is a small cell lung cancer antibody^[8], that can specifically bind with CRMP-5 to form a CV2/CRMP-5 antibody complex. This complex is also called a paratumor antibody and its presence indicates potential tumors. Compared with anti-Hu antibodies, the average survival time of anti-CV2 antibodies in positive patients is significantly longer. The prognosis is good and not affected by tumor types^[9].

AE-merging tumors, known as paratumor-dependent AE, is associated with the limbic system and is classified as PLE. In head MRI examinations of such patients, there is a 66% possibility to find that FLAIR shows high signals in the temporal lobe and hippocampus, indicating that the limbic system is affected^[10]. To date, only one or two cases of antibody-positive paratumor AE have been reported. Approximately 50% of patients developing anti-GABA-BR antibody-positive AE are easy to merge tumors, mainly small cell lung cancer, melanoma, or thymus tumor. For such patients, AE

symptoms often occur before the tumor is diagnosed. However, at present, there is no report that all the above four antibodies are positive at the same time. Compared with the two antibodies, the positive diagnosis of three or more antibodies was difficult. Combining clinical performance of the patient in this case, imaging examination, history of lung cell carcinoma and related antibody results, according to the relevant diagnostic criteria^[10], it is clear that the patient is diagnosed with anti-CV2, anti-Hu, anti-GABA-BR, anti-GAD antibody-positive paraneoplastic autoimmune limbic encephalitis. However, in this case, the patient was also considered (due to his fever) to possibly have viral encephalitis in the early stages, before the results of autoimmune antibodies and paraneoplastic-related antibodies were known. Moreover, a recent study reported that viral encephalitis can be a secondary trigger of AE^[11].

Immunotherapy, including intravenous glucocorticoids and intravenous immunoglobulin administration, is currently indicated for all patients with first-episode AE, with intravenous glucocorticoids as the preferred regimen^[12-15]. In general, treatment with a combination of glucocorticoids and immunoglobulins should be administered. If there is no significant improvement after 2 wk on both first-line immunotherapy, intravenous rituximab should be initiated. There are no clear guidelines for the treatment of paraneoplastic AE, but because of the similarity of many pathogenic mechanisms and antibodies, treatment of paraneoplastic AE is similar to that of AE associated with anti-neuronal cell surface or synaptic protein antibodies, but it should be noted that in T cell-mediated paraneoplastic AE (*e.g.*, anti-Hu antibody-associated encephalitis), irreversible neuronal damage can occur early and rapidly and therefore may respond poorly to immunotherapy^[16-18].

CONCLUSION

In summary, clinical patients who are suspected to have PLE should first undergo related antibody testing and imaging examination to search for evidence of extracranial tumors as early as possible. Early treatment can often achieve better results. However, it should be noted that some clinical cancer patients may appear to have the first

secondary tumor-related antibodies or exhibit negative results for AE antibodies. For such patients, we need to follow them closely and review timely in order to reduce missed diagnosis. For patients who are positive for the antibodies but have no related imaging evidence of tumors, the screening of specific systemic tumors can be carried out according to the positive antibody results.

ORIGINALITY REPORT

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PRIMARY SOURCES

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