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MISLEADING DETECTION OF HERPES SIMPLEX VIRUS TYPE 1 IN A PATIENT WITH PARANEOPLASTIC ENCEPHALITIS

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ABSTRACT

Encephalitis is a potentially life-threatening condition with infectious or autoimmune aetiologies. Autoimmune encephalitis includes paraneoplastic variants associated with specific onconeural antibodies such as anti-Hu, frequently linked to malignancies. Herpes simplex virus type 1 (HSV-1) is the leading infectious cause in adults. Differentiating between these aetiologies can be challenging.

We report the case of an 88-year-old woman admitted with confusion following a fall. Initial evaluation showed clinical signs consistent with encephalitis. During hospitalisation, a seizure was witnessed. Cerebrospinal fluid (CSF) analysis revealed mild pleocytosis, but no infectious agent was detected, and brain imaging revealed no significant abnormalities. After initial improvement under antiepileptic therapy, the patient experienced worsening cognitive dysfunction. Repeat CSF testing 4 weeks after initial symptom onset showed even milder pleocytosis but was positive for HSV-1 and magnetic resonance imaging showed bilateral hippocampal hyperintensities. Analysis of the first CSF sample retrospectively revealed high-titer anti-Hu antibodies. Positron emission tomography-computed tomography scan identified a hypermetabolic lung lesion and para-aortic lymph node, with biopsy confirming the diagnosis of small cell lung cancer. Immunosuppressive and oncologic treatment led to transient improvement, followed by progressive neurological deterioration. Supportive care was ultimately prioritized. This case underscores the diagnostic challenges of encephalitis, especially when autoimmune and infectious features overlap, and diagnostic findings are misleading. Detection of HSV-1 should not delay the investigation of alternative causes of encephalitis in the absence of typical HSV-related features. Early recognition of paraneoplastic encephalitis is critical, as neurologic symptoms may precede the diagnosis of underlying malignancy.

KEYWORDS

Anti-Hu antibodies, encephalitis, herpes simplex virus type 1, small cell lung cancer

LEARNING POINTS

- Onconeural antibodies, such as anti-Hu antibodies, are an under-recognized cause of encephalitis and should be specifically tested for when an autoimmune encephalitis is clinically suspected.
- Detection of anti-Hu antibodies mandates a comprehensive malignancy workup.
- A positive herpes simplex virus type 1 polymerase chain reaction in cerebrospinal fluid does not definitively confirm active infection and must always be interpreted in conjunction with the patient's clinical presentation.

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INTRODUCTION/BACKGROUND

Encephalitis is defined as inflammation of the brain, typically presenting with altered mental status, confusion, fever, focal neurological signs, and seizures. Its aetiology is broad, primarily classified into infectious and autoimmune. The latter can be further subdivided into paraneoplastic, idiopathic, and postinfectious forms[1]. Paraneoplastic encephalitis is associated with onconeural antibodies with anti-Hu antibodies being among the most studied. Paraneoplastic encephalitis is caused by a T-cell-mediated autoimmune response against neuronal antigens, triggered by their ectopic expression in the tumour[2]. Anti-Hu is linked to a malignancy in 80-90% with approximately 80% of malignancies being small cell lung cancer (SCLC) since nearly all SCLC express Hu[3,4].

Herpes simplex virus type 1 (HSV-1) is the most common cause of infectious encephalitis in adults worldwide and requires immediate treatment. Diagnosis typically involves cerebrospinal fluid (CSF) analysis showing pleocytosis (predominantly lymphocytes) and HSV-1 detection by polymerase chain reaction (PCR)[5,6]. It is well known, that in the early course of disease, PCR may yield false-negative results. High clinical suspicion should prompt empirical treatment and repeat lumbar puncture after a few days if initial testing is negative[7]. False-positive HSV-1 PCR in multiplex panels is rare, with test-specificity exceeding 99%. However, a positive PCR result does not confirm active infection. Minimal or absent pleocytosis reduces the test's positive predictive value[8,9].

Differentiating encephalitis aetiologies can be challenging and requires a multimodal diagnostic approach incorporating clinical presentation, disease course, neuroimaging, electroencephalogram (EEG), and CSF findings[10-13].

CASE DESCRIPTION

An 88-year-old female was admitted to the emergency department following an unwitnessed fall with head trauma and repeated episodes of vomiting. Her medical history included primary biliary cholangitis (treated with ursodeoxycholic acid), chronic polyarthritis (leflunomide), hypothyroidism (levothyroxine sodium), hypercholesterolemia (pravastatin), and arterial hypertension (amlodipine, propranolol). She was a lifelong smoker with a history of more than 72 pack years. Prior to the fall, she had been living independently and was in good general health.

On initial examination, she appeared cachectic and reduced in overall condition, was afebrile, and hemodynamically stable. Neurological examination revealed no focal deficits; however, she was disoriented in time and place. Laboratory tests showed mild anaemia (98 g/l), hyponatremia (129 mmol/l) consistent with syndrome of inappropriate antidiuretic hormone secretion, and normal C-reactive protein (CRP) and leukocyte counts. Cerebral magnetic resonance imaging (MRI) demonstrated no acute pathology aside from mild vascular leukoencephalopathy.

Within 24 hours, the patient experienced a secondary generalized tonic-clonic seizure. EEG showed epileptiform discharges in the right frontotemporal region. CSF analysis revealed mild pleocytosis (12 cells/µl, 100% lymphocytes) and slightly elevated protein (480 mg/l). Multiplex PCR testing of CSF for meningitis/encephalitis pathogens yielded negative results. Antiepileptic treatment with levetiracetam and lamotrigine was initiated. A diagnosis of viral encephalitis without identified pathogen and associated early epileptic seizures was made. The patient's clinical condition improved, and she was discharged after a few days without recurrence of seizures.

Four weeks after discharge, she presented to another emergency department with progressive confusion and somnolence since discharge, along with new-onset anxiety as well as visual and auditory hallucinations persisting for one week. Her son reported no recurrence of seizures. Laboratory tests showed persistent anaemia (112 g/l), hyponatremia (129 mmol/l), mildly elevated CRP (20 mg/l), and leucocytosis (11.6 g/l). Neurological examination demonstrated disorientation to time, place, and situation, visual hallucinations, mild lower limb ataxia, and impaired stance and gait. Repeat CSF analysis again showed mild pleocytosis (6 cells/µl, 100% lymphocytes), elevated protein (541 mg/l), and tested positive for HSV-1 by PCR. Acyclovir therapy was initiated promptly. A brain MRI demonstrated bilateral hippocampal hyperintensities in T2/fluid attenuated inversion recovery *(Fig. 1)*.

Meanwhile, retrospective testing of the initial CSF sample (taken 4 weeks earlier) returned positive for anti-Hu antibodies (titer 1:32,000), raising suspicion of paraneoplastic encephalitis. Chest and abdominal computed

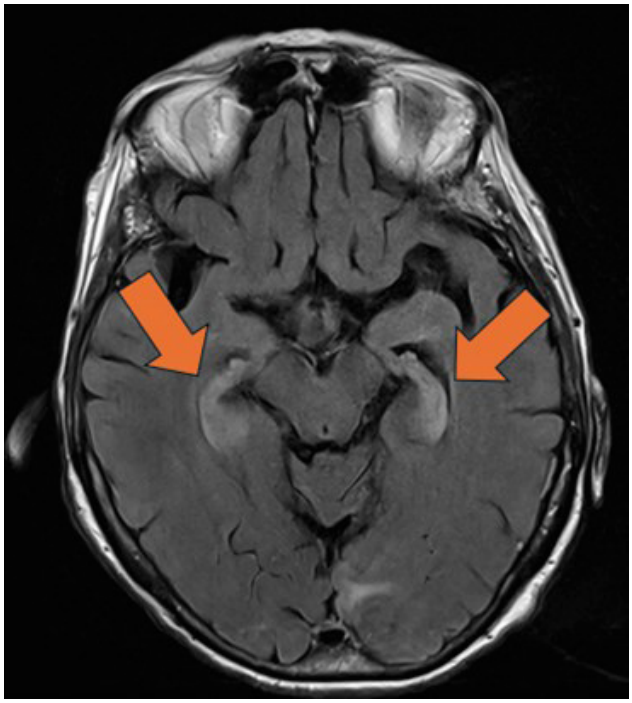


Figure 1. Magnetic resonance imaging showing bilateral hippocampal hyperintensities in T2/fluid attenuated inversion recovery sequence (arrows).

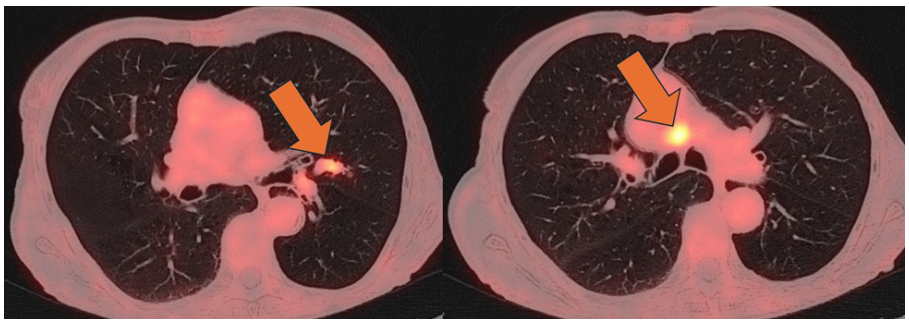


Figure 2. Positron emission tomography-computed tomography with hypermetabolic pulmonary lesion (left, arrow) and hypermetabolic lymph node (right, arrow).

tomography (CT) scan revealed a pulmonary lesion on the right, but a biopsy was negative. The subsequent positron emission tomography-computed tomography (PET/CT) scan showed a hypermetabolic lesion in the left lung and a para-aortic lymph node *(Fig. 2)*. Biopsy of the lymph node confirmed SCLC.

The patient received high-dose intravenous methylprednisolone followed by intravenous immunoglobulin therapy for suspected paraneoplastic encephalitis. Chemotherapy with carboplatin and etoposide was initiated for SCLC. Initial neurological improvement was noted, followed by clinical deterioration. Follow-up imaging at 3 months after treatment initiation showed decreased hippocampal hyperintensities in cerebral MRI and regression of the primary lesion in the lung. Nevertheless, neurological decline continued, and the treatment strategy was ultimately transitioned to best supportive care.

DISCUSSION

Symptoms and clinical evolution are essential in guiding diagnostic reasoning in encephalitis. While CSF PCR testing for pathogens is routinely performed in suspected encephalitis, evaluation for autoimmune causes should be considered when clinical, laboratory and radiological findings are atypical for an infection. Certain distinguishing features between infectious and autoimmune encephalitis exist *(Table 1)*, but accurate diagnosis requires integration of all findings. In the present case, the subacute and fluctuating symptom course over several weeks, combined with persistently mild CSF pleocytosis argued against an active HSV-1 encephalitis. Survival for several weeks without antiviral treatment would be unlikely in HSV-1 encephalitis. Although false-positive HSV PCR results are rare, a positive PCR alone does not confirm clinically relevant infection and should not preclude consideration of an autoimmune process.

Detection of high-titer anti-Hu antibodies, along with the patient's clinical, laboratory and radiological findings, supported the diagnosis of paraneoplastic encephalitis. Given its strong association with malignancies, detection of anti-Hu antibodies should prompt a malignancy workup. Although the initial CT scan and biopsy of a suspicious pulmonary lesion did not confirm malignancy, the high association of anti-Hu antibody with SCLC, together with the patient's smoking history, warranted intensification of the malignancy workup with PET/CT. Even when no malignancy is initially identified in PET/CT, serial screening every 3–6 months is advisable, as paraneoplastic encephalitis may precede the detection of an underlying malignancy[11].

	HSV-1 encephalitis	Paraneoplastic encephalitis (e.g. anti-Hu)
Clinical features/course	Acute onset, rapid progression, high mortality without treatment; altered mental status; focal deficits; fever (>70%); headache; seizures (often focal)	Subacute onset, fluctuating course; cognitive dysfunction (memory loss, confusion); psychiatric symptoms (anxiety, psychosis); movement disorders; seizures
MRI	Unilateral or asymmetric bilateral (especially in severe or advanced disease) T2/FLAIR hyperintensity in mesial temporal lobes, insula, inferior frontal lobes; restricted diffusion; haemorrhage; rarely normal	Medial temporal lobe T2/FLAIR hyperintensity (often bilateral and symmetric); may involve hippocampus, basal ganglia, brainstem, cerebellum; haemorrhage less likely; normal MRI in 15–40% early in the course of disease
CSF	Lymphocytic pleocytosis (typically 10–200/µl, but can be normal); elevated protein; normal or mildly decreased glucose; positive HSV-1 PCR; red blood cells may be present	Mild lymphocytic or absent pleocytosis; mild to moderate protein elevation; oligoclonal bands may be present; negative infectious PCR; paraneoplastic antibodies (e.g. anti-Hu)
EEG	Focal (temporal) or (in severe cases) generalized slowing; epileptiform discharges	Focal or generalized slowing; epileptiform discharges; non-convulsive status epilepticus possible

Abbreviations: HSV-1, Herpes simplex virus type 1; MRI, magnetic resonance imaging; FLAIR, fluid attenuated inversion recovery; CSF, cerebrospinal fluid; PCR, polymerase chain reaction; EEG, electroencephalogram.

Table 1. Typical features of HSV-1 and paraneoplastic encephalitis[6,10-13].

CONCLUSION

This case illustrates the diagnostic complexity of encephalitis and emphasizes that no single finding—not even a positive HSV-1 PCR—should be interpreted in isolation. Early recognition of paraneoplastic encephalitis is crucial, as timely diagnosis and treatment may impact both neurologic and oncologic outcomes.

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