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REVIEW OF DIAGNOSTIC CHALLENGES AND LITERATURE DATA IN PARANEOPLASTIC LIMBIC ENCEPHALITIS: A CASE PRESENTATION

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ABSTRACT

Paraneoplastic limbic encephalitis is a rare condition reported in practice. It is most commonly associated with small cell lung cancer (SCLC). This case report is offered to aid physicians in making informed decisions about timing and type of treatment and is evident, that quick diagnosis is critical for both, neurologists and oncologists. The presentation reviews the case of a female patient diagnosed with limbic encephalitis. Further research is needed to establish clinical, laboratory and instrumental criteria that may be related to outcomes. The purpose of this paper is to present the potential repercussions of a delayed diagnosis and highlight the beneficial results of specific investigations and symptomatic therapy. Comprehensive familiarity with clinical presentations and the limitations of current diagnostic procedures is imperative for neurologists. Equally essential is this understanding for radiologists, serving as the basis for accurate diagnostic analyses derived from imaging findings. The intricate nature of neurological disorders sometimes necessitates the cooperation of neurologists, radiologists, and, in this particular instance, oncologists, in order to achieve precise diagnosis and develop successful treatment approaches.

Keywords: limbic encephalitis, autoimmune disease, small-cell lung cancer, cerebrospinal fluid, prognosis.

Introduction

Paraneoplastic limbic encephalitis (PLE) is a rare neurological condition associated with cancer that primarily impacts the limbic system, including the hippocampus, hypothalamus, and amygdala. Patients typically present symptoms including cognitive dysfunction, personality changes, short-term memory loss and seizures (1).

Paraneoplastic limbic encephalitis is most frequently associated with lung cancer (approximately 50% of PLE cases), and 80% of these cases are small cell lung cancer (2). PLE treatment options include immunotherapy and cancer treatment (3).

Over the last decade, there has been an advancement in our comprehension of the mechanisms underlying Paraneoplastic Limbic Encephalitis (PLE). Research findings indicate that individuals with Limbic Encephalitis and associated tumors generally exhibit lower survival rates compared to those without tumors (4).

We report an overview of the clinical symptoms, diagnostic methods, and treatment options for paraneoplastic limbic encephalitis. It is crucial to identify the context in which Paraneoplastic Limbic Encephalitis (PLE) occurs, especially in cases where it is associated with small cell lung cancer.

Introduction

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Case presentation

The patient was a 66-year old female, without any previous medical conditions, which presented at the Neurology Clinic of 'Sf. Ap Andrei' Emergency County Clinical Hospital (Constanta, Romania) with a sudden onset of speech difficulties. On admission, the neurological examination indicated that the patient was conscious, temporally and spatially disoriented without other signs of neurological impairment at the time. The patient was admitted to the 'Sf. Ap Andrei' Emergency County Clinical Hospital in Constanta, Romania, in August 2023 and was discharged following an 18-day hospitalization period. The native computed tomography (CT) scan of the brain revealed acute ischemic stroke in the temporal lobe under observation and MRI of the brain is recommended. Biological analysis blood tests indicated hyperglycemia (128mg/dl).

At two days after admission, the patient underwent brain MRI, which suggested left hippocampal edematous lesion with possible inflammatory, autoimmune substrate, to be monitored (Figure 1).

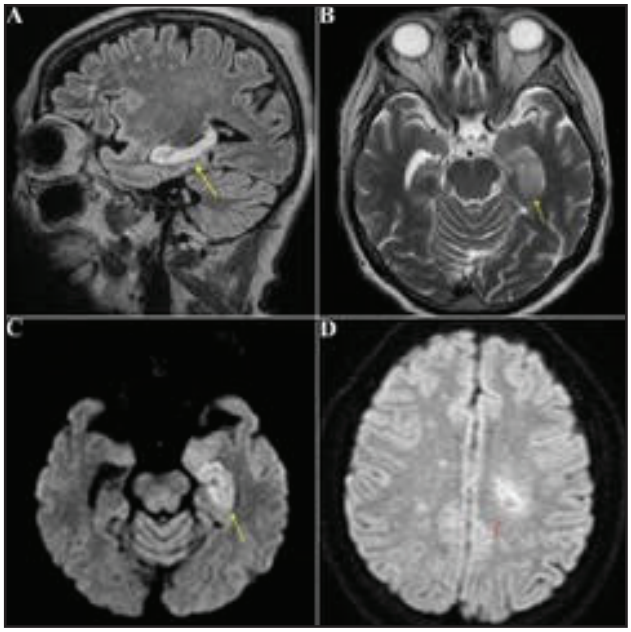

Figure 1. Brain MRI: MRI demonstrates unilateral increased FLAIR (A) and T2 (B) signal intensity of the left mesial temporal lobe; DWI hyperintensity (C) without hypointense correspondent on the ADC map (D).

In the same day, a Doppler ultrasound of the cervical vessels was performed, revealing a stenosis at the origin of the right common carotid artery measuring 48% and an electroencephalogram was made without graphs suggestive of a lesional pathway.

Following a six-day period, a lumbar puncture was conducted. Macroscopically, the cerebrospinal fluid (CSF) appeared transparent and clear. In the complete CSF examination, the results were within the normal range (Table 1).

Table 1. Findings from cerebrospinal fluid analyses.

Parameter	Value	Normal Value
CSF albumin	269	<350
CSF chloride	126	120-130
CSF glucose	75	45-80
Number of elements	4	<=3

1 CSF - cerebrospinal fluid

On day 7 after admission, the neurologist decided to perform anti-neuronal nuclear antibody SOX1(Anti-Sry-like high mobility group box 1), with low level positive. Anti-NMDA receptor antibodies (Anti N-methyl-D-aspartate receptor antibodies), HIV 1+2, RPR, autoantibodies against the voltage-gated potassium channel (VGKC), antibody Herpes Simplex viruses 1 & 2, all test results were negative (Table 2).

Table 2 Results of the laboratory testing

Parameter	Valkue	Normal value
Anti-neuronal nuclear antibody SOX1	Low-level positive	Negative
Anti-NMDA receptor antibodies	Negative	Negative
Autoantibodies against the voltage-gated potassium channel (VGKC)	Negative	Negative
HIV 1+2	Negative	Negative
RPR	Negative	Negative
ANtibody Herpes Simplex viruses 1 & 2	Negative	Negative

On day 9 after admission, a native chest and abdomen computer tomography (CT) scan was performed, native and with gadolinium-based contrast substance revealed left basal dorsopleural thickening, bronchiolitis, pleuro-pulmonary fibrotic changes, pulmonary micronodules with fibrotic sequelae, mediastinal lymphadenopathy, hepatic cysts, liver pseudonodular areas, and bilateral adrenal adenomas.

The following day, a mammogram was performed, revealing a focal asymmetry in the right breast categorized as Birads 3. The recommendation for further investigation included a breast ultrasound.

The breast ultrasound described both breasts with fibrous structure, bilateral glandular tissue with fibroadenomatous features. No space-occupying formations were identified, indicating no suspicion of a carcinomatous process. No detectable axillary lymph nodes bilaterally on ultrasound. Classified as Birads 2 - typically benign changes.

Fourteen days after admission, the patient underwent a brain MRI, which suggested a regressing left hippocampal edematous lesion (Figure 2).

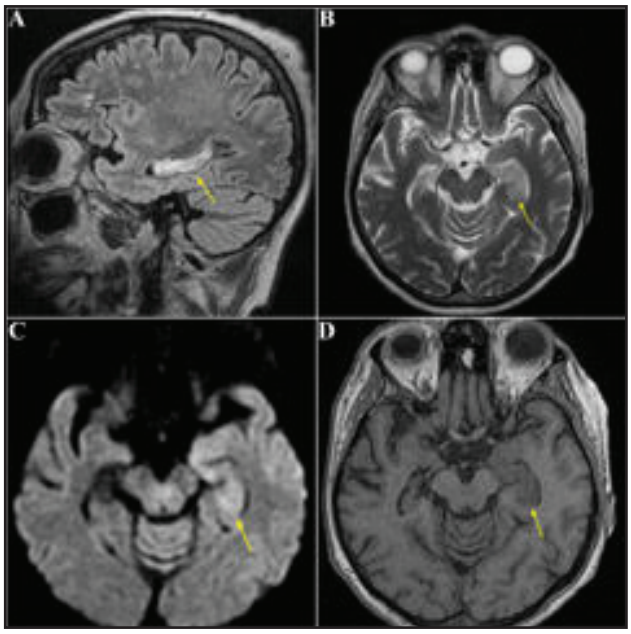

Figure 2. Brain MRI: Three weeks after first brain MRI, there is a decrease in the hiperintensity on FLAIR (A) and T2 weighted (B) imaging in the left medial temporal lobe; DWI shows slight reduction in intensity (C) as does the T1 imaging (D).

Seventeen days after admission, the tumor markers CEA (carcinoembryonic antigen), NSE (neuron-specific enolase) and CYFRA 21-1 (cytokeratin fragment 19) were collected with increased values (Table 3).

Table 3 Values of tumor markers

Parameter	Value	Normal Value
CEA (carcinoembryonic antigen)	15.9	<3
NSE (neuron-specific enolase)	17.1	<17
CYFRA 21-1 (cytokeratin fragment 19)	7.3	<=3.3

On day 18 after admission, based into consideration the results of blood and imaging investigations, with the patient clinical course, the diagnosis was paraneoplastic limbic encephalitis, possibly related to a pulmonary neoplasm. At the time of discharge, the patient was conscious, partially oriented in time and space and showed no other signs of neurological impairment.

Discussion

The majority of individuals presenting Paraneoplastic Limbic Encephalitis (PLE)

typically have an associated cancer, commonly found in the lungs, thymus gland, ovaries, breasts, or testes. In rarer instances, other types of cancers may trigger this condition. The prognosis heavily relies on the specific underlying tumor and the exact manifestation, often categorized by the involved antibodies. In certain cases, if the cancer is identified and effectively treated, there may be an improvement or at least stabilization of the condition. Unfortunately, in many instances, treatment does not ameliorate the patient's neurological symptoms, possibly due to irreversible damage inflicted by the immune system on the brain cells, and successful control of the tumor becomes challenging (4).

The case presented a 66-year-old woman with no previous medical conditions. During the 18-day hospitalization period, various diagnostic procedures were performed; the patient underwent brain MRI, which suggested left hippocampal edematous lesion with possible inflammatory, autoimmune substrate.

A series of tests were conducted, encompassing anti-neuronal nuclear antibody SOX1 with low level positive. Anti-NMDA receptor antibodies, HIV 1+2, RPR, autoantibodies against the voltage-gated potassium channel (VGKC), antibody Herpes Simplex viruses 1 & 2, all test results were negative. Lumbar puncture was performed, In the complete CSF examination, the results were within the normal range.

Fourteen days after admission, the patient underwent a brain MRI, which suggested a regressing left hippocampal edematous lesion. The tumor markers CEA (carcinoembryonic antigen), NSE (neuron-specific enolase) and CYFRA 21-1 (cytokeratin fragment 19) were collected with increased values.

At the time of admission, patient assessments included determining, recent exposure to COVID-19 and his vaccination status against SARS-CoV-2 infection. The pandemic that resulted from the spread of SARS-CoV-2 viral infections has affected the population worldwide but has characteristically shown a preponderance for affecting adults (5, 6).

In the case of the presented patient, he has not been vaccinated during the pandemic and has not recently experienced symptoms that would raise suspicion of SARS-CoV-2 infection. Neurological diseases, particularly those associated with demyelination and inflammation, pose substantial challenges in terms of diagnosis and subsequent management. Accurate diagnosis plays a pivotal role in guiding therapeutic decisions, facilitating disease monitoring, and optimizing patient outcomes (7).

The differential diagnosis was made with acute disseminated encephalomyelitis (ADEM); however, the distribution of the lesions on the MRI did not align. The typical involvement sites can be identified on the brain and cervical spine MRI, performed native and with gadolinium-based contrast substance, indicates the presence of demyelinating lesions. These lesions are observed intracerebrally, encompassing both infratentorial and supratentorial regions, as well as in the cervical and dorsal spinal cord. Given all the evidence and a careful differential diagnosis, the final diagnosis was Paraneoplastic limbic encephalitis.

The prompt diagnosis of neurological conditions and the adoption of an appropriate differential diagnosis process are critical for both neurologists and patients. Neurological disorders comprise a broad spectrum of conditions, such as stroke, multiple sclerosis, and Parkinson's disease, as well as rare disorders and syndromes (8-10). These conditions can have substantial implications for patients' quality of life and long-term prognosis. Early detection of these instances enables immediate and targeted intervention, guaranteeing that patients can promptly obtain appropriate treatment to control symptoms, reduce the progression of the disease, or even stop the advancement of the condition. Moreover, a thorough differential diagnostic approach is crucial for neurologists to effectively discriminate between numerous neurological conditions that may present with identical symptoms. This method allows clinicians to accurately determine the specific root cause of the symptoms, leading to more efficient treatment strategies and improved patient care. Early diagnosis and the use of relevant differential diagnosis techniques are advantageous for both neurologists and patients. These practices lead to increased clinical results, improved symptom management, and an overall higher quality of life

for those suffering from neurological illnesses (7, 11, 12).

Conclusions

The prompt diagnosis of paraneoplastic limbic encephalitis is crucial, particularly in determining its etiology. Initiating targeted treatment promptly is essential for the long-term prognosis of patients diagnosed with this condition. Ongoing research is being conducted to understand the complex relationship between these disorders and to discover diagnostic markers that might assist in differentiating between them.

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