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Case Report
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Autoimmune limbic encephalitis combined with leptomeningeal metastases of non-small cell lung cancer: treatment response to osimertinib, immunoglobulin, rituximab, and tocilizumab

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When a patient with encephalopathy has an organic brain lesion, his symptom is easily and often mistakenly attributed to that brain lesion. However, a combination of different conditions is also possible. We present a case of autoimmune limbic encephalitis combined with leptomeningeal carcinomatosis. A 57-year-old female patient was transferred to our institute with a 1-month history of seizure and aggressive behavior. Subacute onset of psychosis with multifocal T2 high signal lesions suggested autoimmune encephalitis, and high-dose steroid pulse and immunoglobulin therapy were started. However, a cerebrospinal fluid study revealed metastatic adenocarcinoma of non-small cell lung cancer, of which she was in complete remission state. Osimertinib, a third-generation epidermal growth factor receptor tyrosine kinase inhibitor, was started targeting leptomeningeal metastases while maintaining immunotherapy of rituximab and tocilizumab. Her neurological symptoms showed improvement in response to immunotherapy which lasted approximately 1 month and then deteriorated again. We concluded that her symptoms were more attributable to autoimmune encephalitis than leptomeningeal carcinomatosis, and discontinued osimertinib.

Keywords: Meningeal carcinomatosis, Autoimmune encephalitis, Rituximab, Osimertinib

Introduction

Diagnosis of autoimmune encephalitis requires careful history collection and examination followed by extensive ancillary testing to exclude any other etiology. An organic brain disease is a possible cause of encephalopathy. However, organic brain disease (such as infection, tumor, and stroke) does not exclude having comorbid encephalitis, although such cases are very rare. We present a case of acute onset progressive psychosis and seizure, confirmed to be due to leptomeningeal metastases from non-small cell lung cancer but also suggestive of superimposed autoimmune encephalitis. Her psychotic symptoms responded well to immunotherapy, such as immunoglobulin, rituximab, and tocilizumab.

Case Report

A 57-year-old woman was admitted to the emergency department for subacute onset of aggressive behavior and progressive gait disturbance followed by generalized tonic-clonic seizures in November 2021. She had been diagnosed with stage 1 non-small cell lung cancer (NSCLC) in 2017. After left upper lung lobectomy, she achieved complete remission and under-

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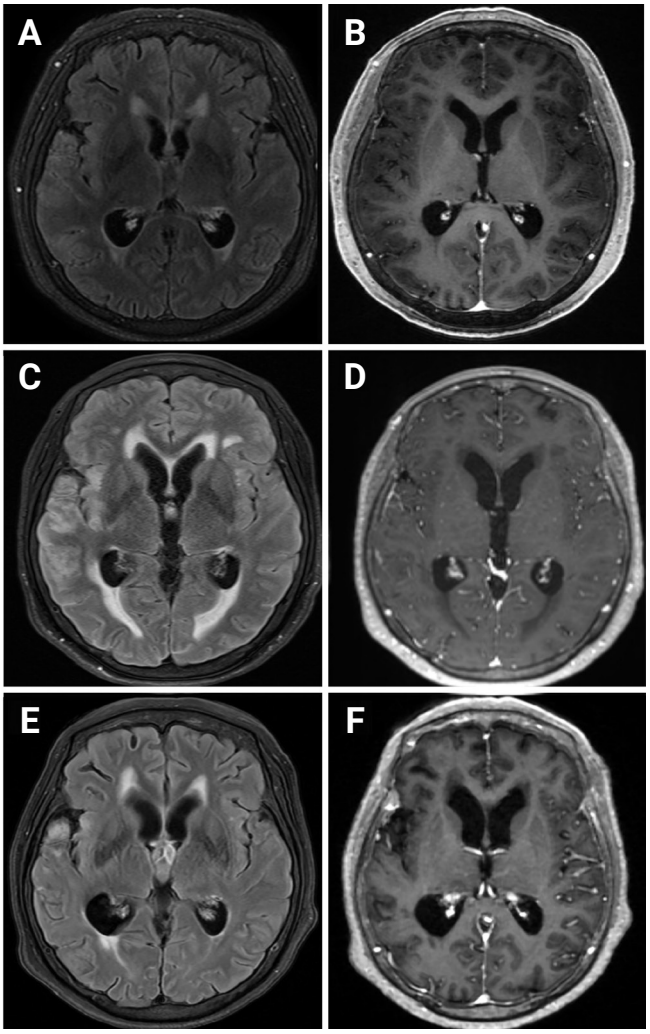
went no additional chemotherapy. The initial brain magnetic resonance imaging (MRI) showed bilateral cortical swelling without definite cortical or leptomeningeal enhancement (Figure 1A and B). A cerebrospinal fluid study showed zero white blood cells, an elevated protein level (92 mg/dL), and severe hypoglycorrhachia (4 mg/dL). The sample was also negative in viral polymerase chain reaction for herpes simplex virus (HSV)-1, HSV-2, and Epstein-Barr virus, as were bacterial cultures.

Figure 1 MRIs of a patient with leptomeningeal metastases with possible autoimmune encephalitis



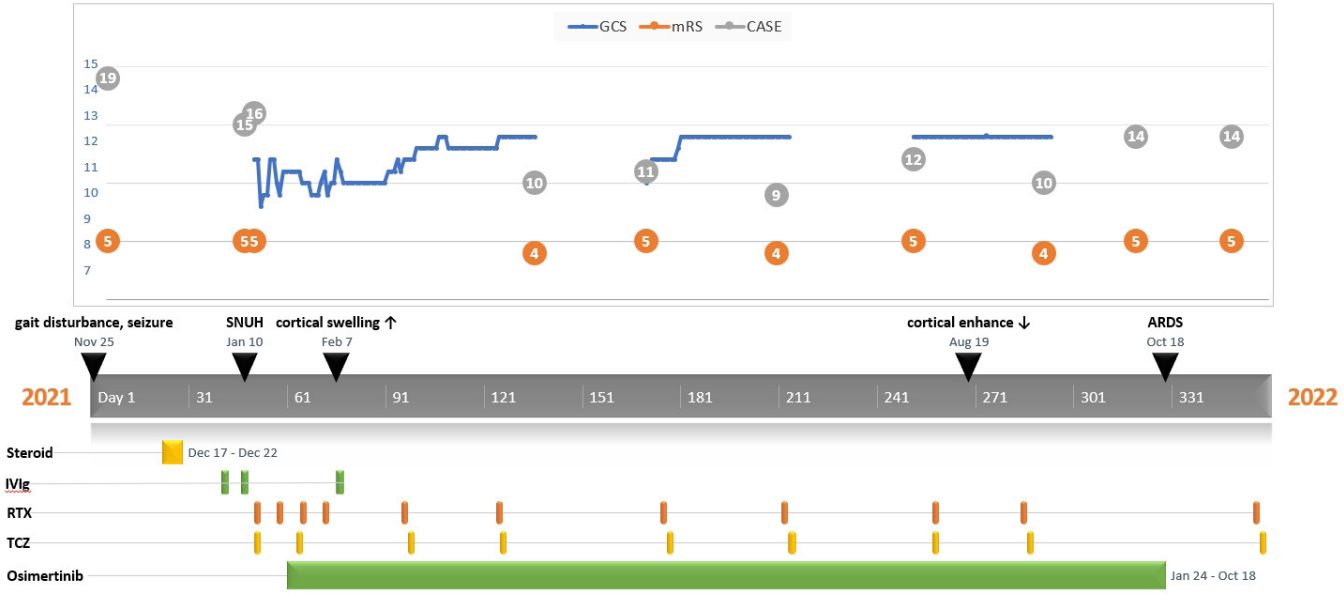
(A, B) The initial brain MRI shows subtle T2 high-signal lesions but no definite leptomeningeal enhancement. **(C)** MRI performed immediately after administration of intravenous immunoglobulin shows increased cortical signals in the right temporal cortex and newly appearing multifocal white matter hyperintensities. **(D)** Newly appearing leptomeningeal enhancement. **(E, F)** MRI was performed after multiple doses of rituximab and tocilizumab.
MRI, magnetic resonance image.

Under the initial impression of possible autoimmune encephalitis (Clinical Assessment Scale in Autoimmune Encephalitis [1] [CASE] score of 19, modified Rankin Scale [mRS] score of 5), a high-dose corticosteroid pulse (1 g/day for 5 days) was administered but produced no clinical response. Subsequent immunoglobulin administrations (0.4 g/kg for 5 days), however, significantly but temporarily diminished the patient's psychotic behavior and aggression (CASE score, 15 and mRS score, 5; 44 hospital days). A lumbar puncture was repeated, and cytologic testing showed metastatic adenocarcinoma. Although whole-body positron emission tomography found no solid malignancy, her physician recommended chemotherapy for carcinomatosis cerebri. At this point, she was transferred to our institution for a second opinion.

Upon arrival at our institution, she was drowsy and unable to follow any commands. Electroencephalogram (EEG) showed ongoing electrographic seizures originating from the bitemporal areas. Due to the patient's aggravating clinical symptoms and progressive swelling evident on brain MRI (Figure 1B and C), she was immediately treated with intravenous immunoglobulin (IVIg) followed by rituximab (RTX; 375 mg/m^2) and tocilizumab (TCZ; 4 mg/kg) (CASE score, 16 and mRS score, 5; 47 hospital days). The lumbar puncture was repeated but revealed only a few malignant cells with epidermal growth factor receptor (EGFR) mutation, confirming leptomeningeal metastases (LM). Autoimmune/paraneoplastic antibodies (NMDAR Ab, CASP2 Ab, AMPA Ab, LGI1 Ab, DPPX Ab, GABAR Ab, Hu Ab, Ri Ab, and Yo Ab) were negative. The patient has been prescribed 80 mg daily of osimertinib, a third-generation EGFR tyrosine kinase inhibitor (TKI), while maintaining weekly RTX and monthly TCZ treatments (Figure 2).

Antiseizure medications (ASM) of lacosamide, levetiracetam, and clobazam were started upon the patient's arrival at our institution. The patient had not experienced convulsive seizures, but EEG consistently showed frequent epileptic discharges despite ASM addition. Her psychosis and seizures gradually improved beginning with the first booster dose of IVIg and subsequent immunotherapies, albeit with daily fluctuations. By the time she finished the sixth round of RTX, the third round of TCZ, and daily osimertinib, she was able to follow simple commands and speak in simple sentences (CASE score, 10 and mRS score, 4; 135 hospital days). She was initially discharged to a local rehabilitation center and readmitted monthly for immunotherapy; at each admission, her daughter complained of neurological deterioration approximately 1 month after RTX. This deterioration was always reversed after

Figure 2 Treatment schedule and progress of clinical assessment scales



The schedule and effect of immunotherapy (steroid, intravenous immunoglobulin [IVIg], rituximab [RTX], and tocilizumab [TCZ]) are represented by clinical assessment scales: the Glasgow Coma Scale (GCS), modified Rankin Scale (mRS), and Clinical Assessment Scale in Autoimmune Encephalitis (CASE). Initial IVIg treatment was effective at reducing psychosis, suggesting an autoimmune pathology. Each dose of RTX and TCZ resulted in an increase in the GCS and a reduction in mRS and CASE scores.
ARDS, acute respiratory distress syndrome; SNUH, Seoul National University Hospital.

the next immunotherapy. This pattern of monthly fluctuation was observed except for the period of acute respiratory distress syndrome (ARDS) that was associated with pneumocystis pneumonia. Osimertinib was discontinued during the period of ARDS but did not affect the neurological status and was eventually withdrawn indefinitely until LM progression should become evident.

Discussion

Autoimmune encephalitis, which remains a diagnosis of exclusion, typically receives little attention when the patient has known organic brain disease, such as neuroinflammatory disease, infection, or carcinomatosis [2,3]. However, the combined condition of such a primary disorder with an autoimmune reaction is also possible. There has been a case report of a nonconvulsive status epilepticus (NCSE) patient with LM and positivity for the SOX1 antibody [4]. His NCSE condition was attributed to SOX1-positive paraneoplastic encephalitis rather than LM, which was limited to his brainstem and was not severe.

In our case, there were several reasons to consider superimposed autoimmune encephalitis even though the patient was confirmed to have LM. First, her mental status improved dramatically with immunotherapy at administration of IVIg and before the first dose of osimertinib. In addition, with subsequent immunotherapies, her symptoms also significantly improved followed by a slow decline until the next dose of immunotherapy. Clinical trials of osimertinib have been conducted in patients with asymptomatic or mildly symptomatic LM [5,6], but its effect on neurological improvement remain unknown. However, considering that the mean time-to-response of osimertinib is 5.9 weeks according to a large clinical trial [7], the immediate recovery of neurological symptoms after treatment should be attributed to a response to immunotherapy rather than chemotherapy.

Second, cortical and subcortical swelling was indicated by areas of T2 high-signal intensity (HSI) compared to that with cortical contrast enhancement. Irritation from LM cells can cause inflammatory swelling in the cortex and subcortex. However, our patient's MRI revealed several patchy T2-HSI areas of paraventricular white matter except in the cortical area. These patchy high signals slowly regressed after immunotherapy. Third, her initial EEGs showed multiple areas of

seizure activity starting from the bitemporal area. According to a study on EEG characteristics in patients with leptomeningeal carcinomatosis [8], the most common characteristic was background slowing, while the most frequent findings were rhythmic periodic patterns and spike wave activity. Ictal recordings were very rare. Although EEG seems to be of little help when differentiating autoimmune seizures from others [9], multiple ictal EEG patterns suggest a widespread, multifocal hyperexcitability that might be explained by an autoimmune etiology [10].

There has been no single standard management for LM of NSCLC; instead, a multidisciplinary effort is typically required for each individual [11]. Treatment options include radiation therapy and systemic or intrathecal chemotherapy. There is a special interest in molecular targeted agents (such as EGFR TKIs or anaplastic lymphoma kinase inhibitors) for select patients with actionable gene mutations. Recently, reports have shown promising effects of immune checkpoint inhibitors, such as nivolumab and pembrolizumab, in LM from NSCLC.

The question could be raised whether RTX and TCZ had antitumor effects in addition to their expected anti-inflammatory effects in our patient. RTX and TCZ have not been considered a conventional option for NSCLC, although there are some ongoing clinical trials of TCZ in combination with other checkpoint inhibitors. TCZ was initially developed as an antirheumatic agent, but only a few reports have shown antitumor effects. One study reported induction of apoptosis of tumor cells in an NSCLC cell culture treated with TCZ [12]. However, as a large monoclonal antibody, TCZ is not expected to penetrate the blood-brain barrier and affect leptomeningeal tumor cells [13]. RTX, a potent CD20 monoclonal antibody, has shown efficient depletion of B cells inside primary lung tumors [14]. However, to our knowledge, RTX has shown no evidence of anti-tumor effects other than in B-cell malignancies.

In conclusion, we present the case of a patient with confirmed LM of NSCLC who demonstrated symptoms suggestive of superimposed paraneoplastic limbic encephalitis. Further study is needed to determine the biological background of the connection between LM and autoimmune encephalitis. It is suggested that clinicians consider all possible diagnoses in such cases.

Conflicts of Interest

Kon Chu has been on the Editorial Board of *encephalitis* since October 2020. He was not involved in the review process of this case report. No other potential conflict of interest relevant to this article was reported.

Author Contributions

Conceptualization: SA, HSL, KC; Visualization, Investigation: SL; Resources: HSL; Supervision: SJA, HSL, KC; Writing–original draft: SL; Writing–review & editing: SJA, KC

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