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Case Report: Anti-AMPAR A1 Autoimmune Encephalitis Following Resection of Multifocal Early-Stage Lung Adenocarcinoma with Exploratory Immunohistochemical Insights

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Case Report

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Abstract

Background:

Anti-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) autoimmune encephalitis is a rare antibody-mediated inflammatory disorder of the central nervous system. Approximately half of reported cases are associated with underlying neoplasms, most commonly thymoma, small-cell lung cancer, and breast cancer. However, its association with lung adenocarcinoma, particularly at an early stage, remains rarely described

Case Presentation:

We report the case of a 38-year-old woman who developed subacute memory impairment approximately six months after undergoing video-assisted thoracoscopic wedge resection for multifocal pulmonary ground-glass nodules. Cerebrospinal fluid (CSF) analyses revealed anti-AMPAR A1 antibody positivity (titer 1:10). Cranial magnetic resonance imaging (MRI) showed no significant abnormalities. The patient demonstrated marked clinical improvement following high-dose intravenous methylprednisolone therapy. To explore a potential paraneoplastic mechanism, exploratory immunohistochemical (IHC) staining for AMPAR A1 was performed on the previously resected lung specimens, revealing scattered, weak cytoplasmic immunoreactivity in a subset of tumor cells.

Conclusion:

This case raises the possibility of an association between early-stage lung adenocarcinoma and anti-AMPAR A1 autoimmune encephalitis. The IHC findings provide preliminary histological clues suggestive of AMPAR-related immunoreactivity in tumor tissue; however, further studies are required to clarify the underlying mechanisms.

Introduction

Anti-AMPAR encephalitis is a rare autoimmune inflammatory disorder of the central nervous system mediated by antibodies targeting the GluA1 or GluA2 subunits of the AMPA receptor[1]. Clinically, it typically presents as a form of limbic encephalitis with subacute onset, characterized by short-term memory impairment, psychiatric symptoms, and seizures[2–4].A substantial proportion of cases are associated with underlying malignancies, with reported tumor prevalence ranging from approximately 50% to 70%. The most commonly associated tumors include thymoma, small-cell lung cancer, and breast cancer[2,5,6]. Accordingly, comprehensive tumor screening and long-term surveillance are recommended in patients diagnosed with anti-AMPAR encephalitis[7].In contrast, the association between anti-AMPAR encephalitis and lung adenocarcinoma—particularly at an early stage—remains poorly

characterized, with only limited cases reported in the literature[8] [8].Here, we report a case of anti-AMPAR A1 autoimmune encephalitis presenting predominantly as subacute anterograde memory impairment in a 38-year-old woman, occurring approximately six months after wedge resection of multifocal early-stage lung adenocarcinoma. To further explore a potential paraneoplastic mechanism, we additionally performed exploratory immunohistochemical analysis on the resected tumor tissue.

Case Presentation

A 38-year-old woman with no significant past medical history was found to have multiple ground-glass nodules in the left lung during routine chest computed tomography (CT) screening(Figure 1). Specifically, a nodule in the left upper lobe (nodule A) measured approximately 4.1 × 3.4 mm, while two nodules in the left lower lobe (nodules B and C) measured 6.8 × 6.5 mm and 6.5 × 4.4 mm, respectively. The patient was asymptomatic with respect to respiratory function.She subsequently underwent video-assisted thoracoscopic wedge resection. Histopathological examination revealed that nodule A was atypical adenomatous hyperplasia (AAH), whereas nodules B and C were adenocarcinoma in situ (AIS), consistent with multifocal primary lung adenocarcinomatous lesions. The disease was classified as pathological stage IA. The postoperative course was uneventful, and no adjuvant therapy was administered.Approximately six months after surgery, the patient was admitted with a five-day history of progressive memory impairment. She reported a history of sustained sleep deprivation and physical fatigue beginning approximately ten days prior to symptom onset. The initial presentation was characterized by gradually worsening recent memory deficits, including difficulty recalling recent events and repetitive questioning. She remained able to recognize family members and perform basic activities of daily living independently. There were no accompanying psychiatric symptoms, such as mood disturbance, hallucinations, or delusions, and no seizures were reported.Cranial MRI performed at a local hospital showed no significant abnormalities. Electroencephalography (EEG) was also performed and revealed no epileptiform activity or other significant abnormalities. Due to progressive symptom worsening, the patient was referred for further evaluation.On admission, neurological examination revealed no focal deficits. CSF analysis demonstrated positivity for anti-AMPAR A1 antibodies (titer 1:10), while other autoimmune encephalitis–related antibodies were negative. Routine CSF parameters and biochemical analyses were within normal limits.Neuropsychological assessment showed a Montreal Cognitive Assessment (MoCA) score of 24/30, a Mini-Mental State Examination (MMSE) score of 24/30, and a Clinical Dementia Rating (CDR) score of 0.5.Based on the subacute amnestic presentation and concordant CSF antibody positivity, a diagnosis of anti-AMPAR A1 autoimmune encephalitis was made.The patient received intravenous methylprednisolone pulse therapy (500 mg/day for 5 days), resulting in marked improvement in memory function. She was subsequently transitioned to oral prednisone with gradual tapering.At the three-month follow-up after discharge, the patient reported a subjective decline in recent memory compared with her post-treatment baseline, accompanied by poor sleep quality and vivid dreaming.Table 1

Table 1: This table is the timeline of this patient's disease course.

Figure1: The left pulmonary nodule surgically removed from this patient.

Figure2: This figure shows the immunohistochemistry results. The third one in the top row and the first one on the bottom left are more suggestive of positive results, while the second one on the bottom right is the negative control.

Discussion

The present case describes a patient who developed subacute, predominantly amnestic symptoms approximately six months after resection of multifocal early-stage lung adenocarcinomatous lesions. The clinical presentation was characterized by progressive impairment of recent memory without seizures, psychiatric disturbances, or focal neurological deficits. This phenotype is consistent with a limbic encephalitis–like presentation and resembles the “autoimmune amnestic syndrome” described in previous reports[9].In this patient, cranial MRI and EEG were unremarkable, whereas both clinical features and CSF antibody testing supported the diagnosis of anti-AMPAR A1 autoimmune encephalitis. This observation is in line with previous studies indicating that neuroimaging findings in anti-AMPAR encephalitis may be normal or nonspecific, and that CSF antibody detection plays a central role in diagnosis[4,10]. In addition, the relatively isolated memory impairment and favorable response to corticosteroid therapy in this case may suggest a comparatively mild clinical phenotype, which has been associated with better outcomes in some reports[11].A potential paraneoplastic relationship between the underlying lung adenocarcinomatous lesions and the subsequent development of autoimmune encephalitis may be considered. Anti-AMPAR encephalitis has been reported in association with various malignancies, particularly thymoma and small-cell lung cancer[2,5]. However, its occurrence in the context of early-stage lung adenocarcinoma, especially following surgical resection, remains poorly documented. In the present case, the temporal interval between tumor resection and neurological symptom onset raises the possibility of a delayed immune-mediated process, although a causal relationship cannot be established.To explore this possibility, we performed exploratory immunohistochemical staining for AMPAR A1 on the resected lung tissue. The results demonstrated scattered, weak cytoplasmic immunoreactivity in a subset of tumor cells. While this finding does not provide definitive evidence of specific antigen expression, it may suggest the presence of AMPAR-related immunoreactivity within tumor tissue. One possible interpretation is that tumor-associated antigens may share certain immunological features with neuronal AMPAR; however, this remains speculative and requires further validation.

The mechanism underlying the delayed onset of neurological symptoms in this case is uncertain. It is conceivable that perioperative factors, including surgical stress and transient immune perturbation, may have contributed to alterations in immune homeostasis. In addition, non-specific triggers such as sleep deprivation and physical fatigue preceding symptom onset may have played a role in modulating immune responses. Nevertheless, these hypotheses cannot be confirmed in the present case.Several limitations should be acknowledged. First, although exploratory immunohistochemical staining demonstrated weak cytoplasmic immunoreactivity in a subset of tumor cells, the staining intensity was

low and its biological significance remains uncertain(Figure 2). Importantly, while negative control staining did not show comparable signals, the absence of parallel analysis using independent positive controls or validated reference tissues limits the interpretability and specificity of the findings.Second, the subcellular localization of the observed staining was predominantly cytoplasmic, which is not fully consistent with the expected membrane-associated distribution of AMPAR-related proteins, raising the possibility of nonspecific staining or altered antigen processing in tumor cells.Third, no comparative analysis was performed using lung adenocarcinoma tissues from patients without autoimmune encephalitis, making it difficult to determine whether the observed immunoreactivity is disease-specific or represents a nonspecific feature of tumor tissue.

Finally, as a single case report, the temporal association between tumor resection and the onset of autoimmune encephalitis does not establish a causal relationship, and further studies incorporating larger cohorts and standardized immunohistochemical validation are required.

Abbreviations

AMPAR	Anti-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
CSF	Cerebrospinal fluid
MRI	Magnetic resonance imaging
IHC	Immunohistochemical
CT	Computed tomography
AAH	Adenomatous hyperplasia
AIS	Adenocarcinoma in situ
EEG	Electroencephalography
MoCA	Montreal Cognitive Assessment
MMSE	Mini-Mental State Examination
CDR	Clinical Dementia Rating

Declarations

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Authors’contributions

W.W. and Y.Y. drafted the manuscript; Z.X. performed specimen analysis; Q.T. and G.Y.conducted literature review; H.L. and X.Z.reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Ethics approval and consent to participate

This case report was conducted retrospectively using data obtained during routine clinical care. Our institutional Research Ethics Committee confirmed that formal ethical approval was not required for this individual case report. Written informed consent was obtained from the patient for participation, and all procedures were performed in accordance with the principles of the 1964 Helsinki Declaration and its later amendments.

Consent for publication

Written informed consent for publication was obtained from the patient, who signed the consent form to approve publication of this case report together with all associated figures.

Competing interests

The authors declare no competing interests.

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Figures

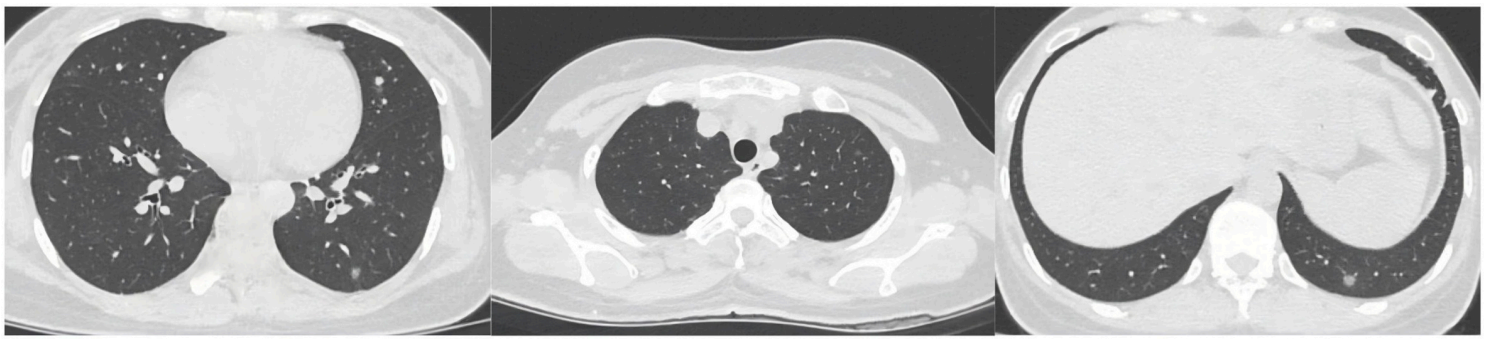


Figure 1

The left pulmonary nodule surgically removed from this patient.

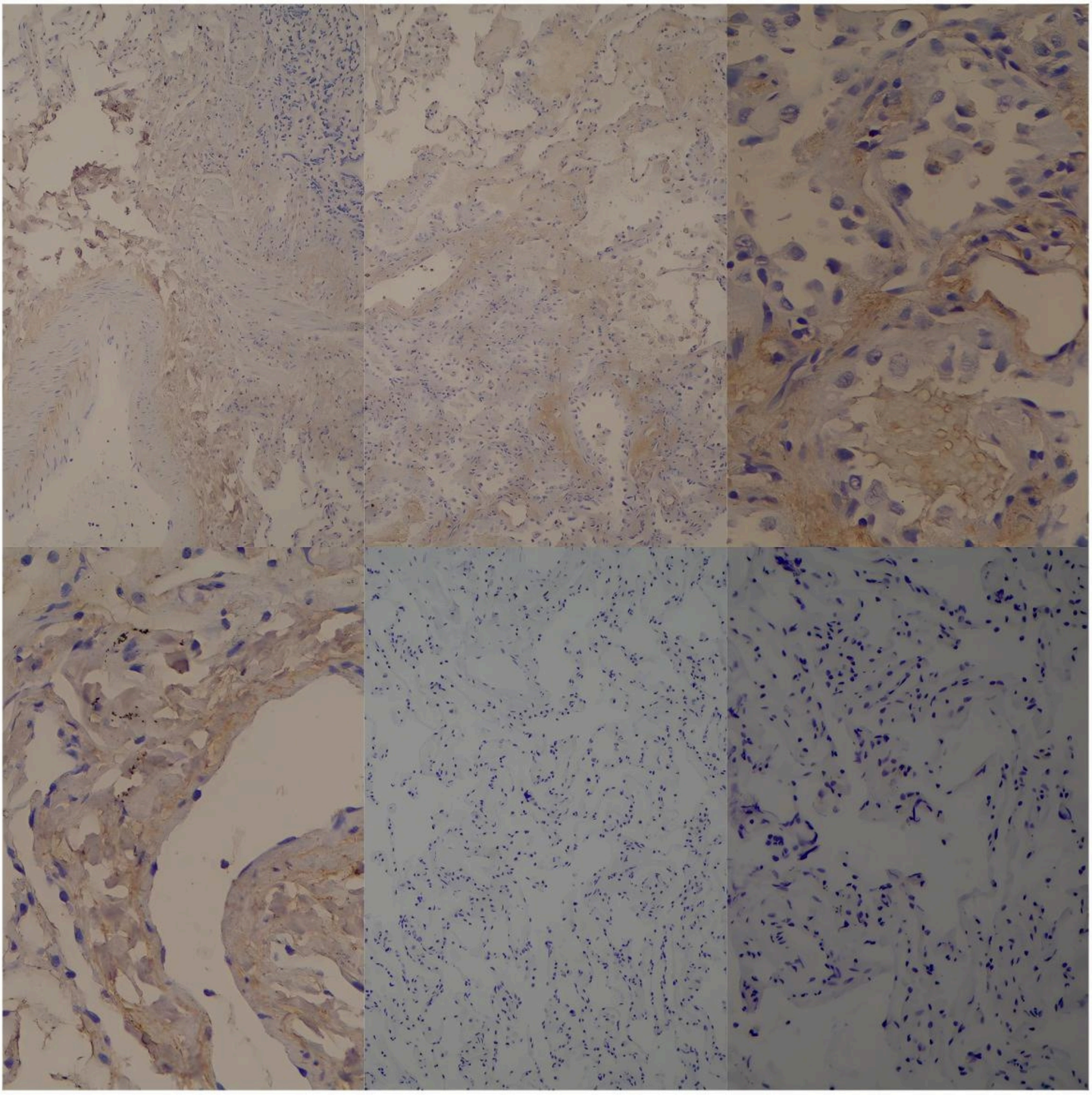


Figure 2

This figure shows the immunohistochemistry results. The third one in the top row and the first one on the bottom left are more suggestive of positive results, while the second one on the bottom right is the negative control.

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