

Anti-SEZ6L2 Antibody-Associated Autoimmune Encephalitis Mimicking Acute Stroke: A Case Report with Literature Review

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Case Report

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Abstract

Background: Anti-SEZ6L2 antibody-associated autoimmune encephalitis is a rare immune-mediated neurological disorder frequently misdiagnosed as cerebrovascular or neurodegenerative diseases due to clinical overlap with stroke and limited disease awareness.

Case presentation: We report a 53-year-old female presenting with acute stroke-like symptoms and patent foramen ovale (PFO), initially misdiagnosed with acute cerebral infarction. The patient developed progressive dysarthria, cerebellar ataxia, cognitive decline, seizures, and psychiatric disturbances. Antiplatelet therapy and PFO closure provided no clinical benefit. Comprehensive workup revealed mildly elevated CSF protein, positive anti-SEZ6L2 antibodies in serum (1:1000) and CSF (1:100), brainstem/somatosensory pathway damage on neurophysiology, and only Fazekas grade 1 white matter hyperintensities on MRI. Immune markers suggested systemic immune dysfunction linked to prior cervical cancer and chemoradiotherapy. The patient stabilized after combined immunotherapy with double filtration plasmapheresis, rituximab, mycophenolate mofetil, and levetiracetam. A systematic literature review with pooled analysis of 24 previously published global cases demonstrated: 70.83% middle-aged/elderly females; core symptoms of cerebellar ataxia (95.83%) and dysarthria (75%); 66.67% with cerebellar atrophy on imaging; 12.50% with paraneoplastic syndrome; and only 58.33% achieving mild symptom improvement after immunotherapy.

Conclusions: This case highlights the necessity of early autoimmune antibody screening for unexplained progressive cerebellar ataxia, particularly in patients presenting with stroke-mimic episodes. Early individualized combination immunotherapy and long-term tumor surveillance are essential for improved prognosis. Further large-scale studies are needed to elucidate pathogenesis and standardize treatment protocols for this rare condition.

Background

In recent years, rapid advances in neuroimmunological detection technologies have facilitated the successive identification of a large panel of pathogenic autoantibodies targeting the central nervous system (CNS), substantially expanding the disease spectrum of autoimmune encephalitis and autoimmune cerebellar ataxia(1). This group of disorders is characterized primarily by dysregulated humoral immunity: aberrantly activated B lymphocytes generate disease-specific autoantibodies that bind to surface antigens on neurons, cerebellar cells and brainstem cells, directly triggering neuronal injury and synaptic dysfunction, which ultimately lead to a broad spectrum of heterogeneous neurological deficits. These immune-mediated encephalopathies frequently present with insidious onset, chronically progressive clinical courses and high recurrence risks, posing major challenges for differential diagnosis in routine neurological practice(2–4).

SEZ6L2 is a critical transmembrane protein abundantly expressed on the surface of cerebellar cells and central neurons, which exerts pivotal physiological functions in neuronal differentiation, synaptic signal modulation, and the maintenance of neural circuit homeostasis. In 2014, Yaguchi et al. first documented that anti-SEZ6L2 antibodies could induce neurological damage(5), after which this rare immune-mediated

disorder has garnered growing scholarly attention. As a novel category of neuronal surface autoantibodies, anti-SEZ6L2 IgG initiates localized immune cascades via binding to its target antigen, with a pathogenic signature distinctly different from classic paraneoplastic cerebellar autoantibodies such as anti-Yo and anti-Hu antibodies. Clinical evidence demonstrates that chronic progressive cerebellar ataxia constitutes the cardinal manifestation of this disease, and pathological lesions can extensively involve the cerebral cortex, extrapyramidal system, brainstem, and autonomic nervous system. A subset of patients develop concurrent malignancies, leading to paraneoplastic syndromes driven by molecular mimicry: cross-reactive immune responses occur between tumoral antigens and neuronal SEZ6L2 protein, resulting in persistent exacerbation of neural injury. Such patients typically exhibit more rapid disease progression and poorer clinical prognoses(6–8).

Restricted by its extremely low incidence, global research concerning this disease has so far been dominated by single case reports and small-sample retrospective analyses. Large-scale cohort investigations remain scarce, and a unified elaboration of its pathogenic mechanisms together with standardized immunotherapeutic regimens have not yet been established. Meanwhile, a proportion of patients may present with acute stroke-like episodes, rendering the disorder highly prone to misdiagnosis as cerebral infarction. Coexistence of patent foramen ovale (PFO) further confounds clinical judgment, which ultimately contributes to ineffective intervention and missed optimal therapeutic windows.

Herein, we report a single case of anti-SEZ6L2 antibody-associated autoimmune encephalitis in a patient with a history of cervical cancer treated with chemoradiotherapy, complicated with systemic immune dysregulation and patent foramen ovale (PFO), who initially manifested with acute stroke-like symptoms. In addition, we systematically collate clinical data from 24 previously published global cases with identical diagnosis to analyze their clinical phenotypes, immune biomarkers, therapeutic regimens and long-term prognostic profiles. This work aims to deepen clinicians' comprehensive understanding of this rare immune-mediated encephalopathy, lower the rate of clinical misdiagnosis, and provide clinical evidence for early screening strategies, individualized combined immunotherapy, and long-term tumor surveillance for this disorder.

Case presentation

Clinical Data and Ethical Approval

A single patient diagnosed with anti-SEZ6L2 antibody-associated autoimmune encephalitis admitted to Punan Branch, Renji Hospital, Shanghai Jiao Tong University School of Medicine was enrolled in the present study. A retrospective analysis was performed based on the patient's complete clinical records, auxiliary examination findings, therapeutic procedures and long-term follow-up data. This study protocol was reviewed and approved by the Ethics Committee of Renji Hospital, Shanghai Jiao Tong University School of Medicine (Approval No. LY2026-015-B). Written informed consent was obtained from the patient and her family members for collation of clinical data and subsequent academic publication. All

procedures conducted in this study were strictly implemented in accordance with the ethical principles outlined in the Declaration of Helsinki.

Case History

The patient was a 53-year-old female who developed insidious dysarthria and cerebellar ataxia without apparent predisposing factors in December 2024, accompanied by no limb weakness, limb numbness, or bowel and bladder dysfunction. She initially sought medical care at a local hospital, where she was tentatively diagnosed with cerebral infarction combined with patent foramen ovale (PFO) based on clinical manifestations and neuroimaging results. Conventional cerebrovascular therapies, including antiplatelet agents, lipid-modulating drugs, and circulation-improving treatments, were administered. Her neurological symptoms only achieved transient relief and then progressed relentlessly. She subsequently received percutaneous PFO closure surgery at a tertiary hospital in the city, yet her neurological deficits failed to ameliorate postoperatively. She was then re-treated with dehydrating and circulation-promoting agents for presumed cerebral infarction at the local hospital, but her clinical status showed no improvement. To clarify the definitive etiology, she was admitted to the Department of Neurology of our hospital on February 13, 2025, for further systematic evaluation and intervention.

Past Medical, Personal and Family History

The patient had a 3-year history of hypertension, which was well-controlled with long-term regular oral sacubitril/valsartan 100 mg twice daily. She denied comorbid chronic illnesses including diabetes mellitus and coronary heart disease. Eleven years prior to admission, she underwent radical surgical resection for cervical carcinoma followed by adjuvant chemoradiotherapy, with satisfactory tumor remission after comprehensive treatment. Malignant neoplasms and chemoradiotherapy regimens are capable of chronically disrupting physiological immune homeostasis, which constitutes a potential high-risk trigger for the onset of autoimmune disorders. The patient was born and had long-term residence in Qidong, Nantong City, Jiangsu Province. She denied exposure to epidemic water or endemic disease areas, high-risk sexual behaviors, cigarette smoking, and alcohol consumption. No hereditary neurological disorders, autoimmune diseases, or malignancies were documented in her family pedigree.

Physical Examination

Vital signs were stable upon admission, and no remarkable abnormalities were identified in cardiac, pulmonary and abdominal physical examinations. Neurological examination revealed clear consciousness with scanning speech. Bilateral pupils were isocoric with a diameter of 3 mm and brisk light reflexes, and spontaneous nystagmus was absent. Left nasolabial fold was flattened, tongue deviated to the left, and pharyngeal reflex was blunted. The neck was supple without meningeal irritation. Motor strength was grade V⁻ in the left limbs and grade V in the right limbs, while limb muscle tone was normal throughout. Superficial sensation was symmetric and intact across the whole body. Bilateral finger-to-nose and heel-knee-shin tests showed unsteady and inaccurate movements, and Romberg's

sign was positive, indicating impaired cerebellar function. Tendon reflexes of four extremities were ++, and bilateral pathological reflexes were positive, consistent with pyramidal tract involvement.

Laboratory Tests: Routine laboratory screening was completed after admission, including complete blood count, urinalysis, liver and renal function, serum electrolytes and folate levels, all of which fell within normal reference ranges. Serological screening for thyroid autoantibodies, antinuclear antibodies, vasculitis-associated autoantibodies, hepatitis B virus, syphilis and human immunodeficiency virus yielded negative results. Further immunological biomarker testing revealed multiple aberrant immune parameters: serum anticardiolipin IgA was elevated at 12.80 APLU/mL; the proportion of double-negative T lymphocytes was 11.23%, exceeding the upper normal limit; serum vitamin B12 concentration was > 1476.00 pmol/L; serum protein electrophoresis demonstrated a mildly reduced γ -globulin fraction accounting for 13.11%. Collectively, these multiple abnormal immune biomarkers indicated systemic immune dysregulation in this patient.

Lumbar Puncture and Cerebrospinal Fluid (CSF) Analysis: CSF laboratory results were as follows: white blood cell count 5.00×10^6 /L, glucose 3.27 mmol/L, chloride 128.00 mmol/L, and total protein 0.47 g/L. Mild elevation of CSF protein was observed with normal leukocyte count, while oligoclonal bands were undetectable. No inflammatory features characteristic of central nervous system infectious etiologies were identified.

A comprehensive panel consisting of 33 cerebellar and paraneoplastic autoantibodies was tested, including Hu, Yo, Ri, CV2, Ma1, Ma2, Amphiphysin, PKC γ , Recoverin, Zic4, Tr, Titin, SOX1, GAD65, Homer3, ATP1A3, ARHGAP26, ITPR1, SEZ6L2, mGluR2, mGluR1, GRIK2, KLHL11, NCDN, AP3B2, MAP1B, septin-5, CA8, Rab6A, Rab6B, GRID2, RGS8, and DACH1. As illustrated in Fig. 1, serological testing yielded a positive anti-SEZ6L2 antibody titer of 1:1000 in serum, while cerebrospinal fluid (CSF) anti-SEZ6L2 IgG was positive at a titer of 1:100. The remaining 32 autoantibodies in this panel all returned negative results. Combined with the patient's clinical phenotype, these findings confirmed anti-SEZ6L2 IgG as the pathogenic autoantibody driving the neurological manifestations. Representative antibody staining results are shown in Fig. 1.

Anti-SEZ6L2 IgG antibodies were positive in both serum and cerebrospinal fluid (CSF). **(A1–A3)** CSF anti-SEZ6L2 antibody (1:100 dilution): A1, GFP fluorescence of SEZ6L2-transfected cells; A2, SEZ6L2 antibody fluorescence; A3, merged fluorescence. **(B1–B3)** Serum anti-SEZ6L2 antibody (1:1000 dilution): B1, GFP fluorescence; B2, SEZ6L2 antibody fluorescence; B3, merged fluorescence. The colocalization of green and red signals confirms specific binding of anti-SEZ6L2 IgG to SEZ6L2 protein on the cell membrane.

Neuroelectrophysiological Examinations

A full set of neuroelectrophysiological assessments was performed on the patient on February 18, 2025. As summarized in Table 1, brainstem auditory evoked potentials (BAEP) revealed dysfunction of the left brainstem conduction pathway. Somatosensory evoked potentials (SSEP) of upper and lower extremities

demonstrated impaired afferent conduction in the right upper limb and right lower limb. No remarkable abnormalities were detected in the right median nerve F-waves, routine electromyography, nerve conduction velocities, video electroencephalography or cerebral function monitoring. Collectively, these electrophysiological findings confirmed lesions involving the brainstem and spinocortical somatosensory conduction tracts, which were consistent with the focal neurological signs identified on physical examination.

Table 1
Neuroelectrophysiological findings of the patient upon admission

Examination item	Side	Key waveform	Latency (ms)	Interpeak interval (ms)	Findings
Median nerve SSEP	Left	N20	20.0	-	Abnormal somatosensory evoked potentials of the right upper limb
	Right	N20	21.6	-	
Tibial nerve SSEP	Left	P40	39.9	-	Abnormal somatosensory evoked potentials of the right lower limb
	Right	P40	43.8	-	
BAEP	Left	Waves I, III, V	I:1.9, III:4.4, V:6.4	I-III:2.5, III-V:2.0, I-V:4.5	Abnormal left BAEP
	Right	Waves I, III, V	I:1.9, III:3.8, V:5.8	I-III:1.9, III-V:2.0, I-V:3.9	

Neuroimaging Examinations

Cranial magnetic resonance imaging (MRI) was performed on February 17, 2025. The scans revealed cerebral white matter hyperintensities graded as Fazekas scale 1, with no evidence of acute intracranial infarction, hemorrhage, space-occupying lesions or early cerebellar atrophy. Representative MRI findings are demonstrated in Fig. 2.

Clinical Course, Diagnosis and Prognosis

Localization Diagnosis

Neurological physical examination identified scanning speech, unsteady and inaccurate performance during bilateral finger-to-nose and heel-knee-shin tests, as well as a positive Romberg’s sign, which indicated lesions involving the cerebellum and cerebellar afferent conduction tracts. Concomitant left central facial and lingual palsy, grade V- motor strength in the left lower limb, and bilateral positive pathological reflexes suggested pathological impairment of the brainstem and bilateral pyramidal tracts.

Abnormal brainstem auditory and somatosensory evoked potentials on neuroelectrophysiological testing further validated the involvement of the brainstem and spinocortical somatosensory conduction pathways. Taken together, the multi-modal findings confirmed extensive lesions distributed across the cerebellum, brainstem, pyramidal tracts, and somatosensory conduction pathways.

Qualitative Diagnosis

This middle-aged female patient presented with subacute-onset and progressively deteriorating neurological manifestations, without clinical evidence of toxic, metabolic, infectious or hereditary etiologies. Cerebrospinal fluid (CSF) analysis merely revealed mild protein elevation without prominent inflammatory infiltrates. Cranial magnetic resonance imaging (MRI) excluded structural organic lesions including acute infarction, intracranial hemorrhage, space-occupying masses and severe cerebellar atrophy, thereby ruling out cerebrovascular disorders, neurodegenerative diseases and intracranial neoplasms. Consistent pathogenic autoantibody evidence was obtained, as anti-SEZ6L2 IgG antibodies tested positive in both serum and CSF. Furthermore, her prior history of malignant tumor conferred a predisposing background for autoimmunity and paraneoplastic syndromes. Collectively, the above clinical and laboratory findings established the definitive qualitative diagnosis of anti-SEZ6L2 antibody-associated autoimmune encephalitis.

Therapeutic Interventions and Follow-Up: Stratified combined immunotherapy was administered in accordance with the patient's clinical status following the stepwise immunomodulation strategy. Double-filtration plasmapheresis (DFPP) was initiated on February 20, 2025, delivered once every other day for a total of five sessions. This intervention was performed to eliminate circulating pathogenic anti-SEZ6L2 autoantibodies, proinflammatory cytokines and complement components from both the peripheral circulation and cerebrospinal fluid (CSF). Concurrent oral mycophenolate mofetil at a dose of 0.5 g twice daily was prescribed to suppress aberrant lymphocyte proliferation and modulate systemic immune responses. After completion of the aforementioned regimens, the patient exhibited alleviated dizziness and gait unsteadiness. She was discharged with stable clinical conditions.

After discharge, the patient experienced disease recurrence. In March 2025, she gradually developed cognitive decline and aphasia, with progressive deterioration of neurological deficits. During the disease course, new-onset bladder hemorrhage and hypokalemia occurred sequentially. The patient was transferred to an external hospital for medication adjustment: aspirin and previous antihypertensive agents were discontinued, and the aforementioned complications were controlled after symptomatic management. In October 2025, the patient presented with recurrent bladder hemorrhage. During diagnostic workup, she abruptly developed trismus and upward gaze deviation, which was clinically diagnosed as a seizure episode. Oral levetiracetam was initiated at a dose of 0.5 g twice daily for anti-epileptic therapy, and no further similar episodes occurred thereafter.

The patient was readmitted to our hospital on October 16, 2025. Ambulatory electroencephalography (EEG) performed on October 21 revealed mildly abnormal brain electrical activity. Repeated testing confirmed persistent positivity of anti-SEZ6L2 antibodies in both serum and cerebrospinal fluid. Due to

poor patient tolerance, repeated plasmapheresis was not feasible. Instead, intravenous infusion of rituximab (100 mg) was administered to achieve targeted depletion of aberrantly activated B lymphocytes and thereby halt sustained production of pathogenic autoantibodies. Following treatment, the patient's involuntary head movements showed partial improvement, while other neurological deficits remained largely unchanged.

The patient returned for follow-up evaluation on November 5, 2025. Repeated plasmapheresis was reinitiated on November 11, administered every other day for a total of five sessions. On November 20, an additional intravenous infusion of rituximab (100 mg) was given as consolidation immunotherapy, following which the patient's psychobehavioral abnormalities showed improvement. On December 28, 2025, the patient experienced sudden onset of loss of consciousness and limb convulsions without apparent precipitating factors. Frequent epileptic seizures recurred at intervals of approximately 7–8 minutes, accompanied by vomiting during ictal episodes. Emergency management with intravenous bolus injection of diazepam followed by continuous intravenous infusion effectively controlled seizure activity, with gradual resolution of convulsions. However, involuntary limb movements persisted as a residual neurological deficit.

The patient was admitted to our hospital for the third time on December 29, 2025. Repeat ambulatory EEG on December 31 demonstrated moderately abnormal electrographic activity. The anti-epileptic regimen was adjusted: levetiracetam was up-titrated to 1 g twice daily, and sertraline (0.1 g once daily) was added for management of psychiatric symptoms. Concurrently, comprehensive supportive care was provided, including nutritional support and correction of electrolyte disturbances. Following standardized treatment, the patient's epileptic seizures were effectively controlled, and her overall clinical condition gradually stabilized, leading to hospital discharge.

At the time of the last follow-up, the patient remained on long-term maintenance immunotherapy and symptomatic management. Her overall clinical condition was stable, yet residual neurological deficits persisted, with incomplete recovery of cognitive function, cerebellar coordination, and limb mobility. Given the inherent risk of disease relapse and the patient's history of malignancy, a structured long-term follow-up plan has been established. Ongoing monitoring will include serial measurements of anti-SEZ6L2 antibody titers, serial neurological function assessments, surveillance of tumor-related biomarkers, and regular evaluation for potential treatment-related adverse events. The detailed clinical course and treatment timeline are summarized in Fig. 3.

From disease onset in December 2024 to latest follow-up in January 2026, the patient experienced progressive neurological symptoms with persistent anti-SEZ6L2 antibody positivity. Serial investigations including MRI, neurophysiology, and EEG were performed. Stepwise immunotherapies were administered across three hospitalizations, including double-filtration plasmapheresis (DFPP), mycophenolate mofetil (MMF), rituximab, and anti-epileptic medications.

Discussion

Anti-SEZ6L2 antibody-associated neurological disease is a rare subtype of autoimmune encephalitis that has been increasingly recognized in clinical practice over recent years. The core clinical manifestation is chronic progressive cerebellar ataxia, while pathological involvement may extend to the cerebral cortex, extrapyramidal system, brainstem, and autonomic nervous system. A subset of cases exhibits features consistent with paraneoplastic syndromes. Currently, global research on this condition remains limited to case reports and small-sample retrospective analyses, with a notable lack of large-scale cohort studies and unified standardized diagnostic and therapeutic consensus. Herein, we report a case of anti-SEZ6L2 antibody-associated encephalitis presenting with acute stroke-like onset, complicated by patent foramen ovale (PFO), and with a prior history of cervical cancer treated with chemoradiotherapy. Furthermore, we systematically integrate data from 24 published cases worldwide and conduct a comprehensive analysis covering epidemiological characteristics, immune-mediated injury mechanisms, auxiliary examination features, diagnostic and therapeutic strategies, and prognostic outcomes. This study aims to enhance early disease recognition and improve the standard of clinical diagnosis and management.

Analysis of the pooled data from 24 global cases reveals distinct population distribution characteristics. The disease predominantly affects middle-aged and elderly females, accounting for 70.83% of cases, with an age range of 35–87 years and a mean onset age of 60.1 years. This epidemiological pattern is largely consistent with that of most neuronal surface antibody-mediated autoimmune cerebellar ataxias(5, 8).In terms of clinical phenotype, all patients present with cerebellar ataxia and dysarthria as initial and core symptoms, which represent the most distinctive clinical manifestations of this disorder. As the disease progresses, patients may sequentially develop gait disturbance, cognitive dysfunction, oculomotor abnormalities, and bradykinesia. A subset of patients also exhibits signs of extrapyramidal, pyramidal tract, and autonomic nervous system involvement. This characteristic multisystem involvement renders the disease easily confused with neurodegenerative conditions such as multiple system atrophy (MSA), Parkinson-plus syndromes, and hereditary cerebellar degeneration, posing substantial challenges in clinical differential diagnosis(9). Detailed demographic, clinical, and prognostic characteristics of all 24 cases are summarized in Table 2.

Table 2. Clinical presentations and prognoses of 24 cases of anti-SEZ6L2 antibody-associated disease(5–20)

Characteristic	Value (n, %) or summary statistic
Demographics	
Total patients	24
Sex	Male: 7 (29.17%); Female: 17 (70.83%)
Age, years	Range: 35–87; Mean: 60.08; Median: 58
<50 years	3 (12.50%)
50–59 years	9 (37.50%)
≥60 years	12 (50.00%)
Clinical manifestations	
Cerebellar ataxia	23 (95.83%)
Dysarthria	18 (75.00%)
Cognitive dysfunction	15 (62.50%)
Gait disturbance	15 (62.50%)
Bradykinesia	8 (33.33%)
Nystagmus / abnormal eye movements	8 (33.33%)
Autonomic dysfunction	2 (8.33%)
Other rare symptoms (each)	1 (4.17%)
Cerebrospinal fluid findings	
Abnormal*	12 (50.00%)
Normal	12 (50.00%)
Neuroimaging findings	
MRI abnormalities†	19 (79.17%)
MRI normal	5 (20.83%)
PET/CT abnormalities‡	6/22 (27.27%)
PET/CT normal	16/22 (72.73%)
Therapeutic regimens	
Intravenous methylprednisolone (IVMP)	20 (83.33%)
Intravenous immunoglobulin (IVIg)	19 (79.17%)

Characteristic	Value (n, %) or summary statistic
Demographics	
Rituximab	8 (33.33%)
Plasmapheresis / DFPP	5 (20.83%)
Mycophenolate mofetil	4 (16.67%)
Prednisone	4 (16.67%)
Cyclophosphamide	3 (12.50%)
Other agents (each $\leq 8.33\%$)	≤ 2
Clinical outcomes	
Improved or stable	19 (79.17%)
Worsened or no improvement	4 (16.67%)
Death	1 (4.17%)

***Abnormal CSF was defined as the presence of pleocytosis, elevated protein level, positive oligoclonal bands, or abnormal A β /tau profiles.**

†Abnormal MRI was defined as cerebellar or cerebral atrophy, or abnormal signal intensities on conventional sequences.

‡Abnormal PET/CT was defined as metabolic abnormalities (hypometabolism or hypermetabolic foci) or hypoperfusion; 2 patients had no reported PET/CT data.

Laboratory and neuroimaging examinations serve as important adjuncts for diagnosis but generally lack specificity. In this case series, cerebrospinal fluid (CSF) findings were mostly characterized by mildly elevated protein or completely normal profiles, with no significant increase in cell counts and a low positive rate of oligoclonal bands. This feature may serve as a reference indicator to exclude bacterial and viral infections of the central nervous system as well as typical inflammatory encephalopathies. Cranial MRI findings revealed that 66.67% of patients developed cerebellar atrophy during the disease course, and these radiological changes typically emerged gradually with disease progression. In some patients, only mild white matter changes were visible on MRI at early disease stages, without obvious cerebellar morphological abnormalities—a pattern observed in the present case. Analysis of disease progression patterns suggests that progressive cerebellar atrophy represents a relatively characteristic radiological evolutionary trend(8, 10).PET-CT not only assesses global cerebral metabolic status but also enables screening for occult systemic lesions, conferring important clinical value in high-risk populations with suspected paraneoplastic syndromes(6, 11).Combined serum and CSF anti-SEZ6L2 antibody testing constitutes the core diagnostic criterion for this disease. Notably, positive CSF antibodies more directly confirm targeted antibody-mediated injury to the central nervous system and represent a key basis for distinguishing peripheral immune abnormalities from CNS-specific immune pathology (8, 10).

Paraneoplastic association represents an important clinical attribute of this disease that cannot be overlooked. Among the 24 patients in this pooled analysis, 2 cases were definitively associated with malignancy and 1 case was suspected to be tumor-related, yielding an overall paraneoplastic association rate of 12.50%. From an immunopathological perspective, antigens expressed by tumor cells share structural similarity with SEZ6L2 protein on neuronal surfaces, which can trigger cross-reactive immune responses via molecular mimicry. This mechanism persistently drives pathogenic autoantibody production, leading to progressive neural tissue damage. Clinical observations indicate that patients with concurrent malignancies exhibit more rapid disease progression, poorer response to immunotherapy, and unfavorable overall prognosis(7, 11). The index patient underwent surgery combined with chemoradiotherapy for cervical cancer over a decade ago. The dual effects of the tumor itself and chemoradiotherapy have chronically disrupted immune homeostasis, placing her in a high-risk category for both autoimmune disease and paraneoplastic syndromes. This background provides an immunological explanation for disease onset, recurrent exacerbations, and the development of multiple complications. Therefore, systemic tumor screening should be routinely performed in all patients with positive anti-SEZ6L2 antibodies. For those with a history of malignancy, long-term follow-up protocols should be established to monitor for risks of tumor recurrence or new-onset malignancy.

Currently, no unified treatment protocol exists for this disease, and stepwise combination immunotherapy is widely adopted as the core intervention strategy in clinical practice. First-line therapeutic regimens include glucocorticoid pulse therapy, intravenous immunoglobulin (IVIg), and plasmapheresis, which primarily serve to rapidly clear existing pathogenic autoantibodies, inflammatory cytokines, and complement components, thereby controlling acute immune-mediated injury in the short term. Agents such as rituximab and mycophenolate mofetil are classified as second-line therapy and long-term maintenance regimens: the former achieves targeted depletion of B lymphocytes to fundamentally suppress pathogenic autoantibody synthesis, while the latter exerts sustained regulatory effects on aberrant immune status by inhibiting lymphocyte proliferation. Clinical evidence indicates that single immunotherapeutic agents have limited efficacy. Early initiation of multi-target combination therapy with prolonged treatment courses can effectively delay neurological decline and reduce the risk of disease recurrence(8, 12). In recent years, novel immunotherapeutic agents such as efgartigimod and ofatumumab have been increasingly applied in refractory cases, offering new therapeutic avenues(9, 13). Prognostic data from this pooled analysis of 24 cases demonstrated that, following comprehensive immunotherapy, 58.33% of patients achieved mild symptomatic improvement, 16.67% showed no treatment response, 16.67% experienced progressive disease deterioration, and 4.17% ultimately succumbed to the disease. These findings suggest a moderate overall prognosis for this condition, with early diagnosis and timely initiation of standardized immunotherapy representing the decisive factors for favorable long-term outcomes.

The index patient initially presented with dysarthria and ataxia, which, in combination with her history of patent foramen ovale (PFO), led to repeated misdiagnoses as acute cerebral infarction. She consequently received conventional treatments for cerebrovascular disease, including antiplatelet therapy, circulation-improving agents, and dehydration therapy; transcatheter PFO closure was even

performed. None of these interventions yielded clinical improvement. This misdiagnosis case clearly highlights a persistent clinical challenge: in middle-aged and elderly patients presenting with subacute or chronic progressive cerebellar ataxia, even when cerebrovascular examinations reveal no definite infarct lesions and cranial MRI shows no typical cerebellar atrophy, the diagnostic framework should not be limited to cerebrovascular disease or neurodegenerative disorders. Autoimmune antibody testing can prevent delayed diagnosis and ensure patients do not miss the optimal therapeutic window.

This study has several limitations that should be acknowledged. First, the research is primarily based on a single case combined with a pooled analysis of small-sample published cases, resulting in limited sample size and potential risk of bias in statistical analyses. Second, basic experimental studies were not performed to further validate the specific pathogenic molecular mechanisms of anti-SEZ6L2 antibodies. Third, long-term dynamic monitoring of immune markers and antibody titers in the included patients was not available. Future multi-center, large-scale cohort studies are warranted to further investigate disease pathogenesis, standardize immunotherapy regimens and evaluation criteria, and ultimately refine the comprehensive diagnostic and therapeutic framework for this condition.

Taken together, anti-SEZ6L2 antibody-associated disease is a rare neurological disorder predominantly affecting middle-aged and elderly females. It is characterized by progressive cerebellar ataxia as the core manifestation, multifocal central nervous system involvement, and dual features of both autoimmune disease and paraneoplastic syndrome. Specific antibody testing serves as the gold standard for definitive diagnosis, while progressive cerebellar atrophy represents the characteristic radiological feature. In clinical practice, anti-SEZ6L2 antibody testing should be included in the routine screening panel for patients with chronic cerebellar ataxia of unknown etiology, particularly in middle-aged and elderly populations with concomitant cognitive dysfunction, extrapyramidal impairment, and autonomic dysfunction. Following diagnosis, early initiation of individualized combination immunotherapy is warranted, alongside long-term tumor surveillance, serial neurological function assessments, and monitoring of treatment-related adverse events, with the overarching goal of comprehensively improving patient quality of life.

Declarations

Data availability statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the patient and her family for the publication of this case report. This study was approved by the Ethics Committee of Renji Hospital, Shanghai Jiao Tong University School of Medicine (LY2026-015-B).

Consent for publication

Written informed consent for publication of this case report and any accompanying images was obtained from the patient and her legal representatives. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Author contributions

ZLL: Formal analysis, data curation, writing—original draft. KW, SG, HQW, HYX, MM, HY and YTG: Conceptualization, writing—review and editing, supervision, project administration, funding acquisition. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Generative AI statement

The authors declared that Generative AI was not used in the creation of this manuscript.

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Figures

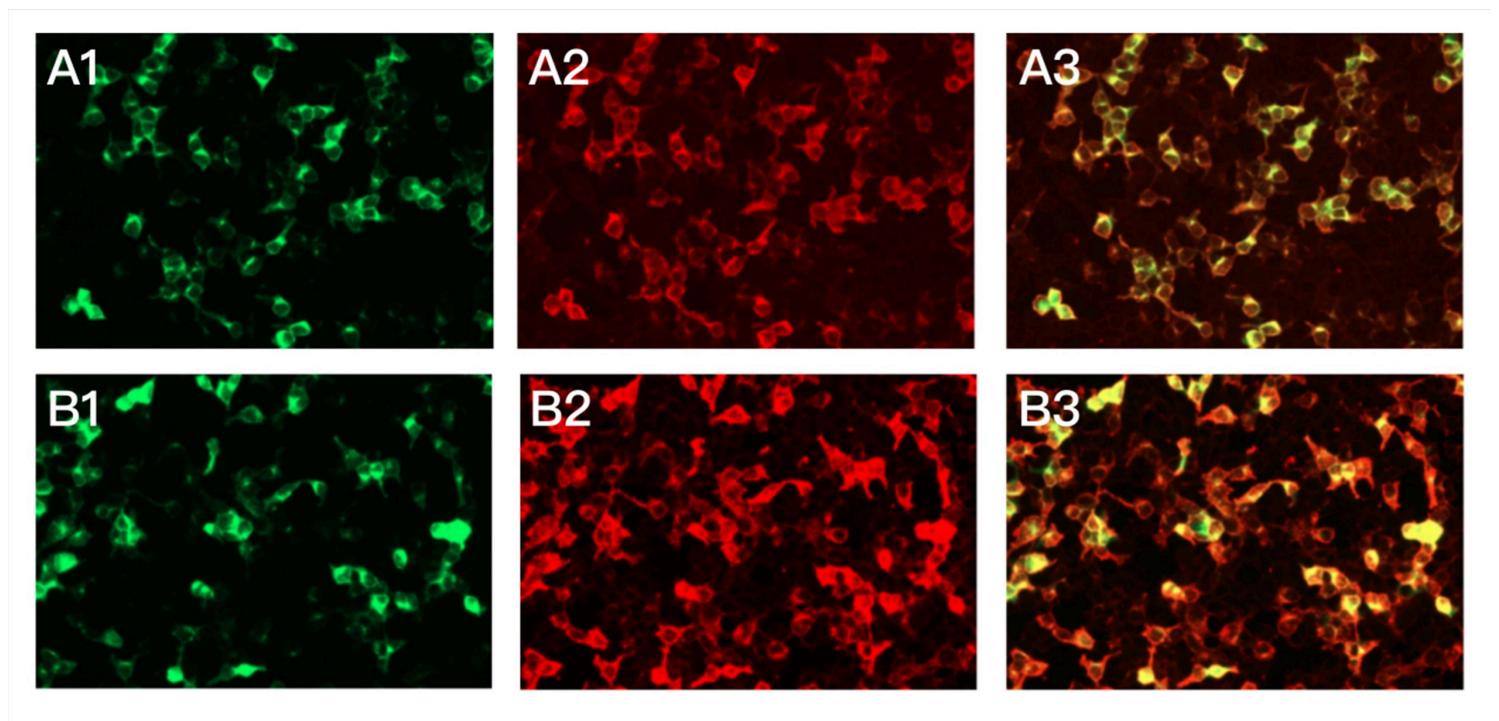


Figure 1

Detection of anti-SEZ6L2 autoantibodies in the patient's serum and cerebrospinal fluid via cell-based indirect immunofluorescence assay

Anti-SEZ6L2 IgG antibodies were positive in both serum and cerebrospinal fluid (CSF). **(A1–A3)** CSF anti-SEZ6L2 antibody (1:100 dilution): A1, GFP fluorescence of SEZ6L2-transfected cells; A2, SEZ6L2 antibody fluorescence; A3, merged fluorescence. **(B1–B3)** Serum anti-SEZ6L2 antibody (1:1000 dilution): B1, GFP fluorescence; B2, SEZ6L2 antibody fluorescence; B3, merged fluorescence. The colocalization of green and red signals confirms specific binding of anti-SEZ6L2 IgG to SEZ6L2 protein on the cell membrane.

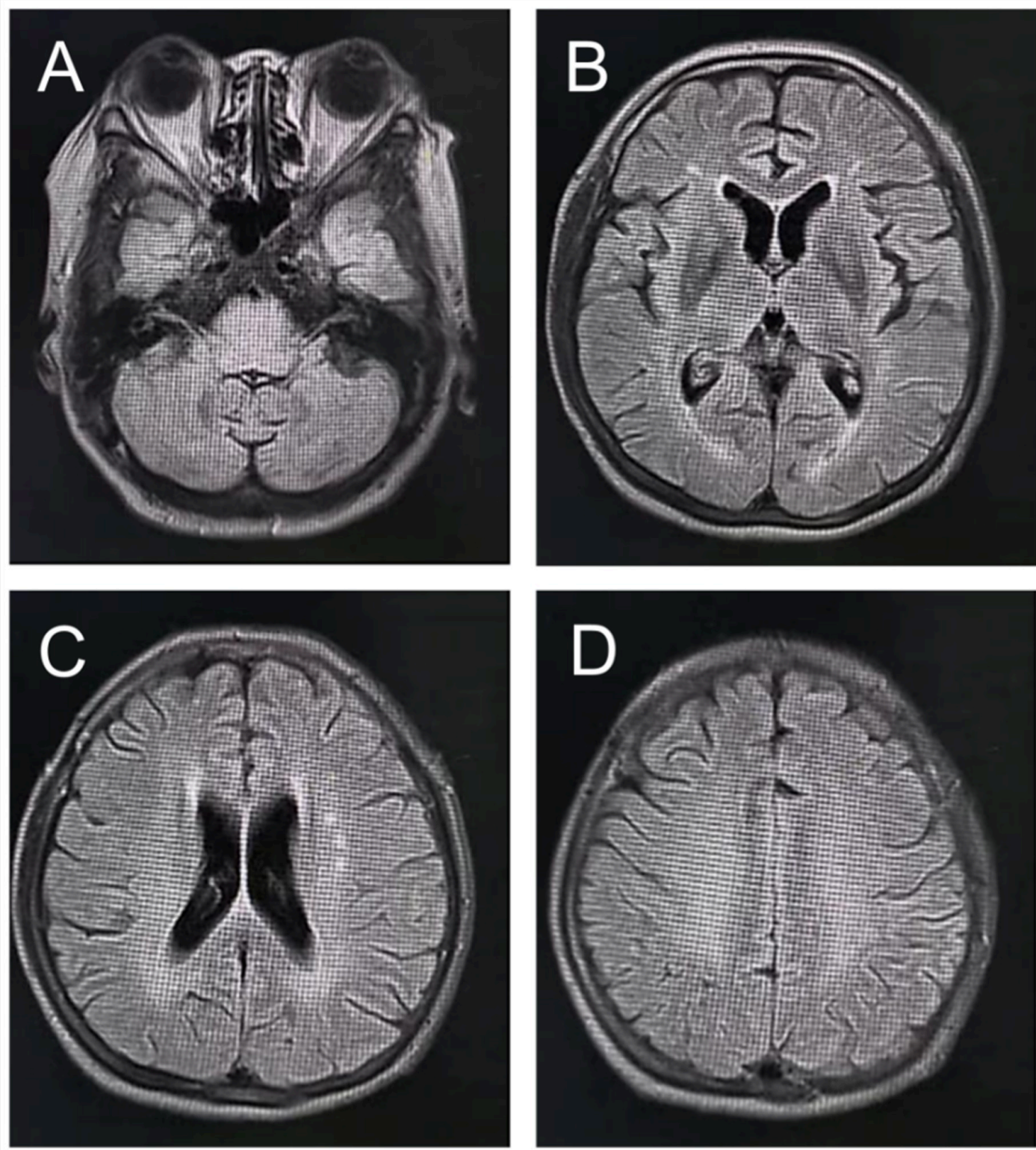


Figure 2

Cranial magnetic resonance imaging manifestations of the patient at admission

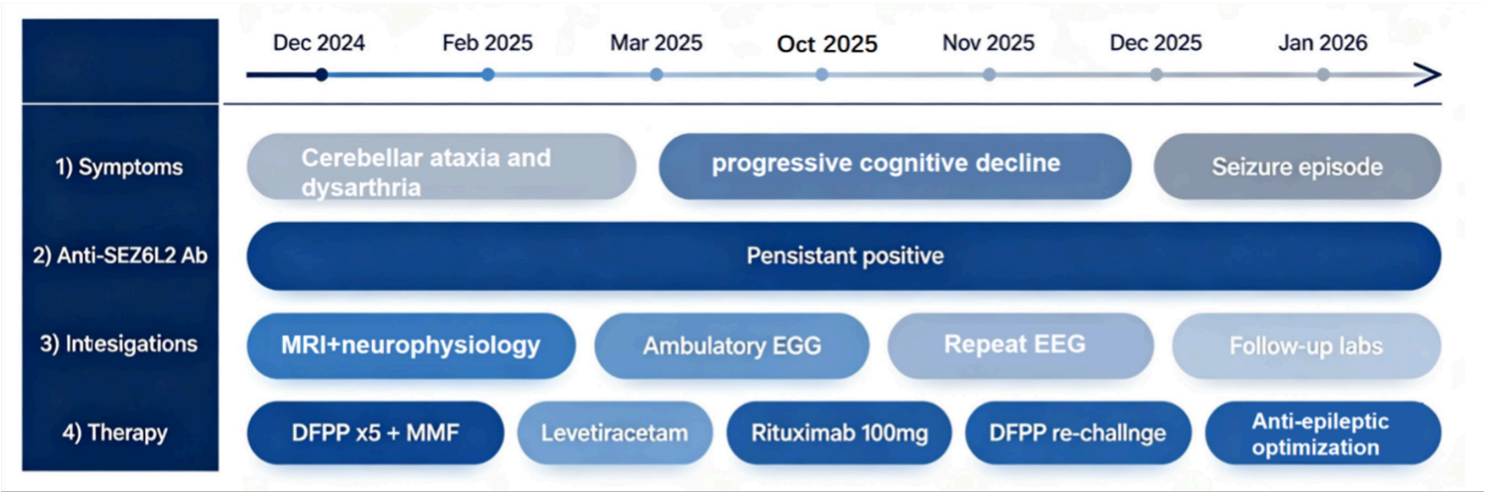


Figure 3

Clinical timeline of disease course and treatment in the index patient.

From disease onset in December 2024 to latest follow-up in January 2026, the patient experienced progressive neurological symptoms with persistent anti-SEZ6L2 antibody positivity. Serial investigations including MRI, neurophysiology, and EEG were performed. Stepwise immunotherapies were administered across three hospitalizations, including double-filtration plasmapheresis (DFPP), mycophenolate mofetil (MMF), rituximab, and anti-epileptic medications.