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CASE REPORT

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Anti-GluK2 antibody-positive autoimmune encephalitis concurrent with multiple myeloma: a case report

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Abstract

Background Autoimmune encephalitis associated with anti-GluK2 antibodies is a recently identified condition, typically characterized by cerebellar ataxia. This case report presents a unique clinical manifestation involving involuntary movements and emotional dysregulation, expanding the known phenotype spectrum.

Case presentation A 60-year-old woman presented with a two-year history of involuntary movements predominantly affecting her lower limbs and facial muscles, occasionally accompanied by hysterical shouting. Initial investigations revealed coexisting multiple myeloma (MM) and anti-GluK2 antibody positivity. Following MM-specific therapy, including bortezomib, cyclophosphamide, and dexamethasone, the patient's symptoms resolved, and her serum anti-GluK2 antibody titers decreased significantly.

Conclusions This case suggests that involuntary movements and psychiatric symptoms may represent novel phenotypes of anti-GluK2 antibody-associated autoimmune encephalitis. The findings underscore the importance of recognizing the diverse clinical presentations of this rare condition and prompt further research into its underlying mechanisms.

Keywords Involuntary movement, Alginate-type glutamate receptor subunit 2 (GluK2) encephalitis, Multiple myeloma

Background

Autoimmune encephalitis refers to a diverse group of inflammatory brain disorders caused by autoantibodies targeting neuronal antigens. Since anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis was first characterized in 2007 [1], the discovery of various novel antibodies has deepened our understanding of this condition. Among these, antibodies against glutamate kainite receptor subunit 2 (GluK2), identified in 2021, represent a rare entity within the glutamate receptor family, which also includes NMDA and AMPA receptors. Functionally, GluK2 plays a critical role in modulating neurotransmitter release at excitatory and inhibitory synapses. Clinically, GluK2-related encephalitis is most often associated with acute cerebellar inflammation, frequently accompanied by MRI T2-FLAIR abnormalities, cognitive dysfunction, epilepsy, corticospinal tract symptoms, or opsoclonus-myoclonus [2].

Multiple myeloma (MM), a malignancy of plasma cells, is characterized by diverse systemic manifestations, including bone lesions, hypercalcemia, renal dysfunction,

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anemia, and multi-organ impairment. Neurological complications of MM are most commonly observed as peripheral neuropathy. In recent years, an increasing number of studies have highlighted the association between autoimmune neurologic disorders and MM, broadening our understanding of its neurological spectrum [3–5]. However, the coexistence of MM and GluK2 antibody-associated autoimmune encephalitis remains undocumented, making this case particularly novel and clinically significant.

Here, we describe a unique case of a patient with MM who presented with GluK2-related autoimmune encephalitis. Treatment targeting MM led to a marked reduction in myeloma cells and serum anti-GluK2 antibody titers, alongside the resolution of neurological symptoms, shedding light on a potential interplay between these conditions.

Case presentation

A 60-year-old woman presented with a two-year history of episodic involuntary movements affecting her lower limbs, which occasionally spread to her upper limbs and facial muscles. Severe episodes involved symptoms such as eye squeezing, lip smacking, chewing motions, slurred speech, and transient unresponsiveness, lasting approximately 10 min. These episodes occurred sporadically, about once or twice annually, but became more frequent and persistent over the two months preceding her admission. The patient reported difficulty walking and feared falling due to these symptoms. She also experienced transient states of unresponsiveness during severe episodes.

Her medical history included chronic glomerulonephritis for over a decade without treatment and long-standing hypertension managed with telmisartan. Upon physical examination, her blood pressure was 103/69 mmHg, pulse rate 92 beats/min, and body temperature 36.1 °C. Neurological assessment revealed normal cerebellar, central nervous system, and extrapyramidal functions. However, bilateral Babinski and Chaddock signs were present. The Mini-Mental State Examination score was 23/30, indicating mild cognitive impairment.

Initial laboratory tests revealed hypoalbuminemia (23.5 g/L; normal range: 40.0–55.0 g/L), hyperlipidemia with elevated total cholesterol (9.27 mmol/L; normal range: 3.11–5.18 mmol/L) and triglycerides (11.11 mmol/L; normal range: 0.56–1.70 mmol/L), elevated D-dimer levels (3.64 μg/mL; normal range: 0.00–0.31 μg/mL), significant proteinuria (urine protein 4+, 10.0 g/L), and abnormal tumor markers including CA125 (48.75 U/mL; normal range: 0.00–35.00 U/mL), CA153 (36.39 U/mL; normal range: 0.00–25.00 U/mL), and CA724 (21.18 U/mL; normal range: 0.00–8.2 U/mL). Blood oxygen partial pressure was reduced (66.8 mmHg; normal range: 80.00–100.00 mmHg). Additional findings included monoclonal gammopathy, confirmed by serum protein electrophoresis showing M protein and immunofixation revealing IgG-λ paraproteinemia.

Neuroimaging(MRI) revealed signs of small vessel disease, while emission computed tomography (ECT) demonstrated pulmonary embolism (PE). Autoantibody testing for demyelinating diseases, autoimmune encephalitis, and paraneoplastic syndromes returned negative results. Cytological examination of cerebrospinal fluid showed no plasma cells. The patient was discharged with a diagnosis of "involuntary movements pending further investigation" and suspected plasma cell disease but declined further testing at the time. Treatment with rivaroxaban for PE was initiated; however, her neurological symptoms persisted.

Six months later, the patient was readmitted due to worsening fatigue and swelling. Repeat laboratory tests revealed severe hypoalbuminemia (19 g/L), markedly elevated urine protein levels (18.64 g/24 h), and a bone marrow biopsy showing 14.5% myeloma cells. Flow cytometry detected monoclonal plasma cells expressing CD27, CD38, CD138, CD200, CD229, CD269, and cκ, but lacking CD19 expression. Fluorescence in situ hybridization (FISH) confirmed the presence of the IGH/FGFR3 fusion gene (40%). A diagnosis of IgG-λ multiple myeloma (MM), ISS stage II, was established.

Given the unexplained neurological symptoms, additional testing for autoimmune encephalitis was conducted, including tissue-based assays (TBA) and extended autoantibody testing with a 16-item cell-based assay (CBA). Results revealed serum positivity for GluK2 antibodies (1:100+) and weakly positive TBA staining in the cerebellum, hippocampus, and cerebral cortex. The findings supported a diagnosis of GluK2 antibody-associated autoimmune encephalitis.

The patient underwent treatment with bortezomib, cyclophosphamide, and dexamethasone. Following two cycles of therapy, her involuntary movements resolved, and she regained normal ambulation. Follow-up testing showed a reduction in urine protein levels (5.66 g/24 h), a decrease in myeloma cell burden, and significantly lower serum GluK2 antibody titers (1:10+). Cerebrospinal fluid GluK2 antibodies were undetectable, and TBA staining remained weakly positive (Figs. 1 and 2).

Discussion

This case represents the first documented coexistence of GluK2 antibody-associated autoimmune encephalitis and multiple myeloma (MM). MM, a plasma cell malignancy, is known for its ability to produce pathogenic antibodies and occasionally trigger paraneoplastic syndromes. However, its association with autoimmune encephalitis

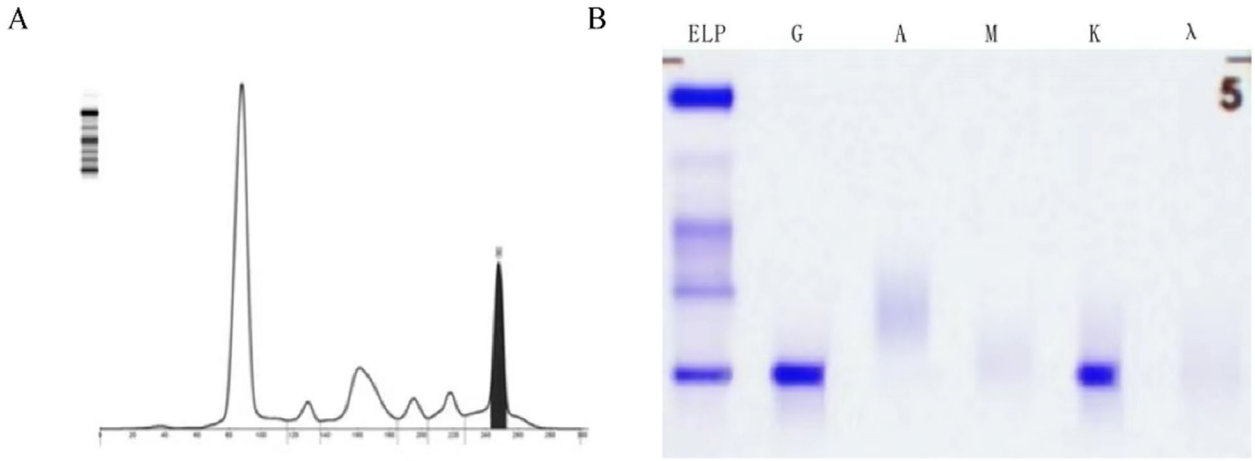

Fig. 1 **A** M protein was seen in serum protein electrophoresis. **B** Immunofixation electrophoresis showed that M protein was IgG-k type

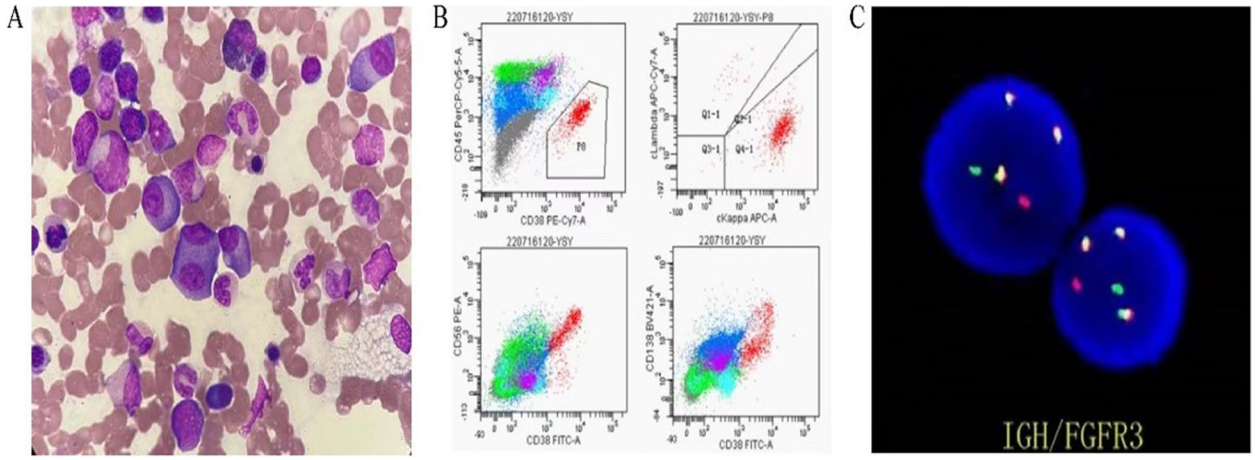

Fig. 2 **A** Bone marrow smear showing dysplasia, with partial binuclear abnormal plasma cells accounting for 14.5% of nuclear cells (1,000x). **B** Flow cytometry showing abnormal plasma cells expressing CD38, CD56, and CD138, with restricted Kappa expression, and no expression of CD19, CD20, MPC1, and CD45, indicating clonal plasma cells. **C** FISH showing that the myeloma cell fusion gene IGH/FGFR3 was positive (40% +)

is exceedingly rare. The remarkable clinical improvement observed in this patient, including resolution of involuntary movements and emotional disturbances following MM-specific therapy, raises intriguing questions about the underlying relationship between these two conditions.

The patient's neurological symptoms, including involuntary movements and psychiatric disturbances, are atypical for GluK2-related encephalitis, which is more commonly characterized by cerebellar ataxia. These unusual symptoms may be explained by the effects of GluK2 antibodies on interconnected neural circuits involving the basal ganglia and cerebral cortex [6]. GluK2, a kainate receptor subunit, is highly expressed in the basal ganglia, particularly in the striatum, which is integral to motor control and emotional regulation. Evidence from animal studies supports the role of GluK2 in these functions. For instance, kainite receptors, including GluK2, have been shown to regulate striatal activity and synaptic circuit development, disruptions of which can result in movement and behavioral abnormalities [7]. Further supporting these observations, Shaltiel and colleagues demonstrated that GluK2 plays a role in controlling behavioral symptoms such as hyperactivity, aggression, and psychomotor agitation in mice, which could relate to the psychiatric features observed in this patient [8]. Additionally, research by Knight et al. has linked genetic mutations in kainite receptors to psychiatric disorders like bipolar disorder and schizophrenia, suggesting a potential mechanistic overlap between GluK2 dysfunction and

human neuropsychiatric conditions [9]. However, these animal models do not fully replicate the complexity of human GluK2 antibody-mediated encephalitis, and their relevance to this patient's clinical presentation remains speculative.

Serological and pathological findings provided critical insights into the pathophysiology of this case. Tissue-based assays revealed weak positivity in the cerebellum, hippocampus, and cerebral cortex, suggesting that GluK2 antibodies may target multiple brain regions. The patient's initial refusal to undergo cerebrospinal fluid (CSF) testing limited early diagnostic confirmation, but subsequent post-treatment analysis demonstrated a decline in serum GluK2 antibody titers and positive TBA results in both serum and CSF. These findings strongly support the involvement of the central nervous system and affirm the diagnosis of GluK2-related encephalitis. The dual therapeutic impact of the bortezomib-cyclophosphamide-dexamethasone (VCD) regimen on MM and GluK2 encephalitis is noteworthy. As a standard treatment for MM, the VCD regimen likely contributed to reducing the antibody titers and alleviating neurological symptoms through its immunomodulatory effects. This raises two possibilities: first, that the improvement in encephalitis symptoms was a secondary outcome of MM therapy; or second, that the GluK2 antibodies were a paraneoplastic phenomenon linked to the plasma cell malignancy.

Despite these insights, many questions remain unanswered. The precise mechanisms by which GluK2 antibodies disrupt neural circuits in humans are not well understood. While animal studies provide valuable evidence of GluK2's role in motor and behavioral regulation, their applicability to human disease requires further investigation. Future research should include human-specific studies and large-scale clinical analyses to elucidate the complex interplay between MM and GluK2 antibody-associated encephalitis.

Conclusions

In conclusion, this case highlights the clinical heterogeneity of GluK2 antibody-associated autoimmune encephalitis and underscores the importance of considering paraneoplastic syndromes in patients with plasma cell disorders presenting with neurological symptoms. The findings contribute to a growing understanding of the diverse phenotypic spectrum of GluK2-related encephalitis and its potential links to systemic malignancies.

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None.

Authors' contributions
CZP, ZSQ and HXR contributed to drafting the manuscript. SXW, XLL and CL contributed to collecting data. ZHL and PX contributed to analyzing the radiological and pathological findings. SY and MSB contributed to critically assessing and revising the manuscript. All the authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The case report complies with all ethics regulations.
This case report was reviewed and approved by the Central Hospital of Dalian University of Technology with the approval number: YN2024-120–01.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Competing interests
The authors declare no competing interests.

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