Clinical Manifestations and Management of Anti-CV2 and Anti-SOX1 Antibody-Positive Paraneoplastic Syndrome: A Case Report

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Abstract

Introduction: Paraneoplastic neurological syndromes (PNS) are rare disorders associated with neuronal antibodies. We report a case of PNS positive for both anti-CV2 and anti-SOX1 antibodies to highlight the diagnostic value of antibody screening in unexplained neurological symptoms.

Case Presentation: A 67-year-old male presented with seizures and cognitive decline. Serological testing revealed positivity for both anti-CV2/collapsin response mediator protein 5 and anti-Sry-like high mobility group box 1 (SOX1) antibodies. Extensive tumor screening revealed no evidence of malignancy. The patient received glucocorticoid pulse therapy.

Results: Following treatment, the patient's clinical symptoms improved significantly, demonstrating a positive response to immunotherapy despite the absence of an underlying tumor currently.

Discussion: This case underscores the clinical relevance of early paraneoplastic antibody testing in patients with acute or subacute neurological deficits. The dual positivity of anti-CV2 and anti-SOX1 antibodies is rare, and this case demonstrates that such syndromes can occur without identifiable tumors and respond favorably to immunosuppression.

Conclusion: Early antibody testing is crucial for diagnosing PNS and guiding individualized treatment strategies, even in tumor-negative cases.

Keywords: cognitive dysfunction; seizures; paraneoplastic syndromes

Introduction

Paraneoplastic neurological syndromes (PNSs) are immune-mediated diseases associated with tumors, typically presenting with seizures, cognitive impairment, and other psychiatric symptoms.[1] The recent identification of anti-CV2 and anti-SRY-like high mobility group box 1 (anti-SOX1) antibodies as new biomarkers

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for diagnosing PNSs has deepened our understanding of autoimmune diseases.[2,3] The presence of these antibodies often indicates an underlying tumor;[1] however, tumor screening may yield negative results in some cases,[4] which complicates clinical diagnosis and treatment.

Anti-CV2 antibodies are usually associated with small-cell lung cancer (SCLC),[2] whereas anti-SOX1 antibodies are linked to a variety of tumor types, including ovarian cancer.[3] Glucocorticoid treatment is widely used to alleviate clinical symptoms of PNSs, particularly in patients who are antibody-positive but tumor-negative during screening.[5]

The co-occurrence of anti-CV2/collapsing response mediator protein 5 (CRMP5) and anti-SOX1 antibodies is rare, and its clinical significance, tumor association, and optimal management remain unclear. Here, we describe such a case. No evidence of tumor was detected during follow-up, and the patient's symptoms improved significantly after glucocorticoid pulse therapy.

Case presentation

As this case report involved no therapeutic research intervention, ethical approval was not required under local legislation and institutional requirements. The patient's legally authorized representative provided written informed consent for participation in this study, and the individual provided written informed consent for the publication of any potentially identifiable images or data included in this case report.

A 67-year-old man was hospitalized in 2023, for seizures that lasted for 3 h. Prior to admission, the patient experienced paroxysmal tonic-clonic seizures characterized by generalized convulsions and loss of consciousness, with these symptoms reportedly lasting 3–4 min before disappearing without any intervention.

The patient had no significant medical history, including trauma, drug ingestion, toxin exposure, or illness. There was no history of alcohol or tobacco consumption and his family history was unremarkable.

On admission, the patient's vital signs showed no notable abnormalities. Laboratory test results, including routine blood analysis, liver and kidney function tests, urinalysis, fecal analysis, thyroid function test, tumor marker measurement, and dynamic electrocardiography, were within the normal range. Serological tests for antibodies against syphilis (*Treponema pallidum* antibodies), hepatitis C virus, human immunodeficiency virus antigen, and hepatitis B surface antigen, yielded negative results. Furthermore, cerebrospinal fluid (CSF) examination revealed a total red blood cell count of 0 and a white blood cell count of 6×10^6/L. CSF biochemistry showed a protein level of 419 mg/L (reference range: 200–400 mg/L), while glucose, chloride, lactate dehydrogenase, and adenosine deaminase levels were all within the normal ranges. The following antibodies were absent in the serum: anti-Hu, anti-Ri, anti-CV2/CRMP5, anti-Amphiphysin, anti-Ma1, anti-Ma2, anti-SOX1, anti-Tr/delta/notch-like epidermal growth factor-related receptor, anti-Zic4, anti-Titin, anti-Recoverin, anti-PKCγ, anti-Yo, and anti-GAD65 antibodies. The following antibodies were absent in both the serum and CSF: anti-NMDA receptor (anti-NMDAR), anti-AMPA1 receptor, anti-AMPA2 receptor, anti-LGI1, anti-$GABA_B$ receptor (anti-$GABA_B$-R), and anti-CASPR2 antibodies. Of note, anti-CV2/CRMP5 and anti-SOX1 antibodies were subsequently detected in the CSF (see below). Video electroencephalography demonstrated mildly abnormal activity, with a background rhythm of 7.7–9.0 Hz and slow waves distributed over the bilateral frontal poles, frontal regions, and frontal midline areas. Chest computed tomography (CT) and cranial magnetic resonance imaging (MRI) findings were normal (Fig. 1).

After admission, the patient experienced seizures every 5–6 days and was diagnosed with epilepsy. The seizure frequency subsided to once every 10–12 days after the administration of sodium valproate sustained-release tablet (0.5 g twice a day). Additionally, the family members reported a marked decline in the patient's memory for 2–3 months after the first seizure, which gradually affected his daily life.

The patient was re-admitted in 2024. Upon admission, neurological examinations revealed impaired cognitive function, manifesting as disorientation and short-term memory deficits. The CSF was re-tested for the presence of paraneoplastic antibodies and was found to be positive for both anti-CV2/CRMP5 and anti-SOX1 antibodies (Fig. 2).

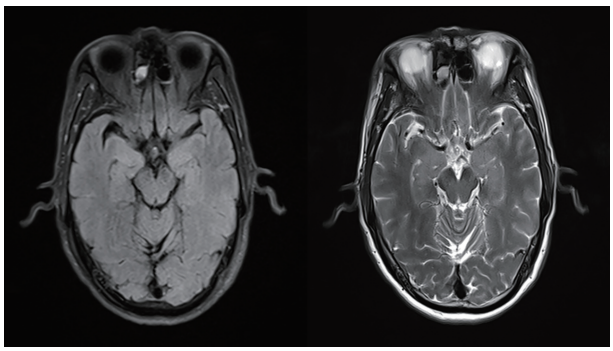


Figure 1: Axial brain MRI [T2-FLAIR (left) and T2WI (right)] showing no evidence of cortico-subcortical atrophy, brain metastasis, or leptomeningeal lesions in this patient presenting with seizures and cognitive decline.

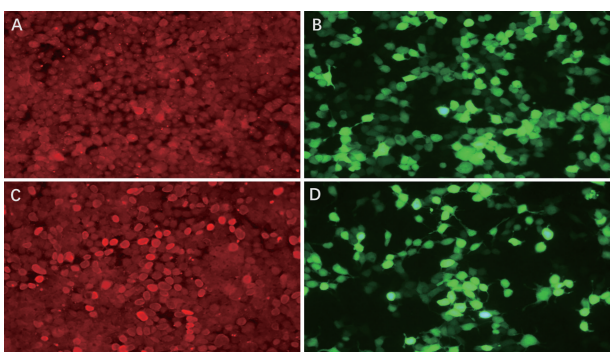


Figure 2: Reactivity of the patient's CSF against CV2 and SOX1 using a live cell-based assay.

(A and B) Anti CV2/CRMP5. (C and D) Anti-SOX1 antibodies.

This finding is noteworthy because the initial serum antibody testing during the first admission was negative for both anti-CV2/CRMP5 and anti-SOX1 antibodies. A diagnosis of PNS was made based on the clinical symptoms and antibody findings. Other potential causes were ruled out carefully.

Comprehensive tumor screening, including abdominal CT and tumor biomarker tests (carcinoembryonic antigen, alpha-fetoprotein, prostate-specific antigen, neuron-specific enolase, and cancer antigens [CA-125, CA19-9, and CA72-4]), yielded negative results. Repeated brain MRI did not show any abnormalities. PET-CT was strongly recommended but declined by the patient due to financial constraints.

Seizures and cognitive impairment are nonspecific presentations that may occur in autoimmune encephalitis, limbic encephalitis, neurodegenerative diseases, and primary epileptic disorders. Autoimmune encephalitis was excluded by negative serum panels for anti-NMDAR, anti-LGI1, and anti-$GABA_B$-R antibodies, in conjunction with normal CSF cell counts and the absence of oligoclonal bands. Limbic encephalitis was considered but was not supported by MRI findings; no T2/FLAIR hyperintensity in mesial temporal structures was observed. Neurodegenerative etiologies were deemed improbable given the subacute symptom evolution and lack of antecedent progressive cognitive decline. Primary epilepsy did not explain the cognitive involvement or the concomitant seropositivity for onconeural antibodies. The presence of anti-CV2/CRMP5 and anti-SOX1 antibodies, combined with the temporal profile and negative workup for alternative entities, substantiated the diagnosis of PNSs.

The patient subsequently received glucocorticoid pulse therapy and continuous glucocorticoid treatment for maintenance. The immunotherapy regimen was as follows: methylprednisolone was administered intravenously at 500 mg/day for three consecutive days, followed by methylprednisolone at 240 mg/day for 2 days; then, the transition to oral prednisone acetate (60 mg/day) for 2 weeks was made, with a subsequent dose tapering schedule (5 mg reduction every 2 weeks) until a maintenance dose of 10–20 mg/day was reached, with subsequent adjustments based on the clinical response. The seizures stopped 5 days after treatment initiation. Cognitive function improved notably (mini-mental state examination score improved from 13 to 19 after 20 days of treatment).

Given the inability to perform PET-CT, a structured follow-up screening strategy was adopted, consisting of repeated physical and dermatological/systemic examinations, repeated chest and abdominal CT every 3 months during the first year and every 6 months thereafter, repeated tumor biomarker measurement at each follow-up visit, and regular neurological and oncological follow-up.

Discussion

This case underscores the complexity of PNSs, particularly in cases with overlapping antibody positivity.

The simultaneous presence of anti-CV2/CRMP5 and anti-SOX1 antibodies is rare, and this case provides additional clinical evidence regarding the presentation, diagnostic workup, tumor screening strategy, and treatment response in such patients. Importantly, the initial antibody testing was negative. This finding suggests that a negative initial antibody result does not exclude PNS or autoimmune encephalitis, and that repeated antibody testing should be considered when clinical suspicion persists.

The simultaneous presence of several antibodies may reflect a hyperactive immune response, which may be associated with several hypothetical possibilities, as discussed below.

Immune cross-reactivity: Different antibodies may target similar antigenic epitopes, leading to cross-reactivity.[6] This phenomenon is relatively common in autoimmune diseases and may account for the concurrent presence of anti-CV2 and anti-SOX1 antibodies in this case. Additionally, cross-reactivity may be influenced by the patient's response to steroid therapy or clinical symptoms, as this may contribute to overall immune dysregulation.

Potential for minuscule tumor foci: Despite negative tumor-screening results in this case, the presence of antibodies suggests underlying minuscule lesions or early tumors. Previous studies indicate that some antibody-positive patients may develop tumors during follow-up.[7] The average time of CV2/CRMP5 neuropathy onset is approximately 185 days prior to cancer diagnosis.[8] However, in our case, cancer was not detected up to 15 months after the first seizure.

Widespread activation of the immune system: PNSs can lead to hyperactive immune system activation, prompting the production of multiple antibodies. The immune response may be a reaction to tumor-associated antigens, even in the absence of identifiable tumors on imaging. Hyperactive immune activation may present as neuropathy, myelopathy, encephalitis, cerebellar ataxia, myasthenia gravis, choreoathetosis, optic neuritis, Lambert–Eaton syndrome, cognitive dysfunction, or psychiatric symptoms.[9]

In our case, the patient showed improvement following corticosteroid treatment. Corticosteroid dosage for PNSs can be personalized, considering symptom severity, overall health, comorbidities, and potential side effects.

Clinically, a high suspicion of PNSs with an initial negative autoimmune antibody screening adds complexity to the case, requiring long-term follow-up and re-evaluation. Furthermore, overlapping antibody positivity suggests that highly complex immune-mediated mechanisms complicate disease management. Clinicians should consider comprehensive assessments to promptly identify potential tumor development or other immune-related diseases. Regular follow-up is recommended every 3–6 months after the initial diagnosis. During follow-up, clinical assessments, imaging tests (CT or MRI), blood tests (including tumor biomarker detection), and neurophysiological examinations may be performed to monitor clinical symptoms and the development of potential tumors.

Clinicians who face patients with similar presentations, or who encounter unexplained neurological, dermatological, or systemic symptoms alongside a known or suspected malignancy should conduct timely antibody testing and provide individualized treatment to enhance patients' quality of life.

Conclusion

This case emphasizes the importance of early antibody testing, especially in conditions of seizures and cognitive impairment, and adopting individualized treatment and follow-up strategies.

Author contributions

Jiayu Liu: conceptualization, writing-original draft preparation; Lanjun Li: data compilation, literature search, writing-review and editing; Wenju Li: Literature search, writing-review and editing; Fengying Li: literature search, writing-review and editing; Jinming Han: conceptualization, writing-review and editing. All authors have read and approved the final version.

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Ethics statement

Ethical approval was not required for the case report in accordance with the local legislation and institutional requirements (No therapeutic research intervention was conducted in this case). Written informed consent for participation in this study was provided by the participants' legally authorized representative. Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this case report.

Data availability statement

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

AI statement

The authors declare that no generative artificial intelligence (AI) or AI-assisted technologies were used in the preparation, analysis, or writing of this manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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