Letter to the Editor

Imaging-negative CV2/collapsin response mediator protein 5 antibody-related paraneoplastic myelopathy: a rare and challenging diagnosis

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Introduction

Paraneoplastic neurological syndrome (PNS) is an uncommon condition that occurs as a result of the immune system mistakenly attacking the central and peripheral nervous systems in response to cancer. It is a rare occurrence (1), affecting only about 0.01% of all cancer patients, and accounts for approximately 10% of non-metastatic neurological complications. Interestingly, around 50% to 80% of PNS cases develop before the cancer diagnosis is conducted (2). PNS encompasses a wide range of neurological disorders that can be classified as either "classic manifestations" (56.0%) like encephalomyelitis, limbic encephalitis, and subacute cerebellar degeneration, or "non-classic manifestations" (44.0%) such as optic neuritis, chorea, and necrotizing myelopathy (1,3). Within PNS (4), there exists a particularly rare subtype known as paraneoplastic myelopathy (PNM).

The diagnosis of PNS is aided by the detection of specific antineuronal antibodies in both serum and cerebrospinal fluid (CSF) (5,6). This helps determine the paraneoplastic origin of neurological syndromes. One such antibody, known as aquaporin-4 antibody (AQP4-Ab), is frequently identified in people who have neuromyelitis optica spectrum disorder (NMOSD), which is an autoimmune myelopathy. Various other autoantibodies, such as anti-CV2/collapsin response mediator protein 5 (CV2/CRMP5), antineuronal nuclear autoantibody (ANNA), amphiphysin, purkinje-cell cytoplasmic autoantibody (PCA), glutamic acid decarboxylase 65 (GAD65), and tripartite motif-containing protein 46 (TRIM46), have also been identified in patients with PNS. These autoantibodies may lead to immune-mediated myelopathy and present similar clinical symptoms to NMOSD (7,8). Most occurrences of PNS involve patients who are negative for serum AQP4-Ab, while seropositive AQP4-Ab is uncommon in patients with paraneoplastic NMOSD (9,10). Magnetic resonance imaging (MRI) scans of the spinal cord in patients with PNS typically show T2 signal abnormalities, which are frequently characterized by severe lesions spanning long segments of the spinal cord (7). However, there have been few reported instances of PNS where spinal MRI images appear normal.

Case presentation

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or

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national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal. A 66-year-old woman was admitted to the neurology department due to progressive limb numbness and difficulty walking. The numbness initially started in the lower extremities 3 months ago and spread up to the knees 2 months prior to admission. The patient also experienced unsteady gait but was still able to perform daily activities without assistance. The neurological examination revealed mild instability while walking, abnormal heel-to-shin testing, a positive Romberg's sign, reduced right foot movement, and a positive Babinski's sign on the right side. There were no signs of muscle weakness in the upper and lower extremities.

During the initial hospital visit, the patient underwent a comprehensive examination to investigate the cause of her paresthesia. It was revealed that she had no history of alcohol or tobacco use, and there was no information provided regarding previous infectious diseases, exposure to toxins, or family illnesses, except for hyperlipidemia. The initial evaluation consisted of various imaging tests including a brain MRI with T1, T2, and fluid-attenuated inversion recovery (FLAIR) sequences, brain diffusion-weighted imaging (DWI), and a spinal cord MRI covering the cervical, thoracic, and lumbar segments. None of these tests showed any significant abnormalities. Further investigations on nerve conduction revealed slightly lower amplitudes for compound muscular action potentials (CMAP) (5.2 *vs.* 8.6 mV for abductor pollicis brevis) and sensory action potentials (SNAP) (33.1 *vs.* 52.7 μV) of the right median nerve branches.

The viral screening results showed that there were no signs of hepatitis B and C viruses, rubella virus, treponema pallidum, human immunodeficiency virus (HIV), and toxoplasma gondii. Additionally, the etiology of the viral infection was excluded because serum samples were tested positive for immunoglobulin G (IgG) antibodies but negative for immunoglobulin M (IgM) antibodies for cytomegalovirus, varicella zoster virus, and Epstein-Barr virus infection. Inflammatory markers such as erythrocyte sedimentation rate, C-reactive protein, white blood cell count, lymphocyte, and neutrophil levels, were all within the normal range. Tests for thyroid function and autoimmune diseases came back negative. Serum levels of IgG, IgM, folic acid, and vitamin B12 were normal. Routine laboratory examinations, including liver function tests (glutamic-pyruvic transaminase, glutamic oxalacetic transaminase), kidney function test (creatinine), muscle enzyme test (creatine kinase, creatine kinase isoenzyme myocardial band), and coagulation testing [D-dimer and fibrinogen degradation products (FDP)] showed no abnormalities. The blood tumor markers, such as alpha-fetoprotein, carcinoma antigen (CA)-125, CA-153, CA-199, CA72-4, neuron-specific enolase, and carcinoembryonic antigen, were all found to be within normal ranges. A chest computed tomography (CT) scan revealed the presence of small nodules in the upper and middle lobes of the right lung, which were determined by experienced radiologists to be chronic inflammatory nodules. An abdominal CT scan showed the existence of a small cyst in the left lobe of the liver. Ultrasonography did not detect any venous thrombus in the upper and lower extremities or structural abnormalities in the superficial lymph nodes in the neck area. As a result, the patient was discharged without a definite diagnosis. Due to the possibility of peripheral neuropathy, the patient was treated with vitamin B12 for a duration of 1 month.

The condition of the patient worsened during the follow-up visit, and the growing numbness in her lower limbs had begun to affect her ability to walk steadily. She was consequently readmitted to the hospital. A neurological test revealed that she had dysmetria (reduced capacity to measure distances), clearly uncoordinated movements, and a mild weakness in her right lower leg (rated 4 out of 5). A positive Babinski's sign was seen on both sides, and the patient also had abnormal sensations (paresthesia) in the trunk and both lower limbs below the T4 level. The patient also had excessive reflexes in both lower limbs. Myelopathy was thought to be a possibility, but repeated MRI scans of the spinal cord and brain showed no aberrant anatomical changes or signals (shown in *Figure 1A-1C*). According to laboratory testing, D-dimer levels (3.8 μg/mL) and FDP levels (41.10 mg/L) were significantly increased. Blood clots were found in the left posterior tibial vein and the right popliteal vein during a subsequent ultrasound test, indicating a hypercoagulable condition. However, compared to the earlier values from 1 month ago, there were no appreciable alterations in the tumor markers and serum immune indices. Upon analysis of CSF, parameters such as cell count, protein content, and glucose concentration were all found to be within normal ranges. There were no signs of oligoclonal bands or antibodies to AQP4, myelin oligodendrocyte glycoprotein (MOG), or glial fibrillary

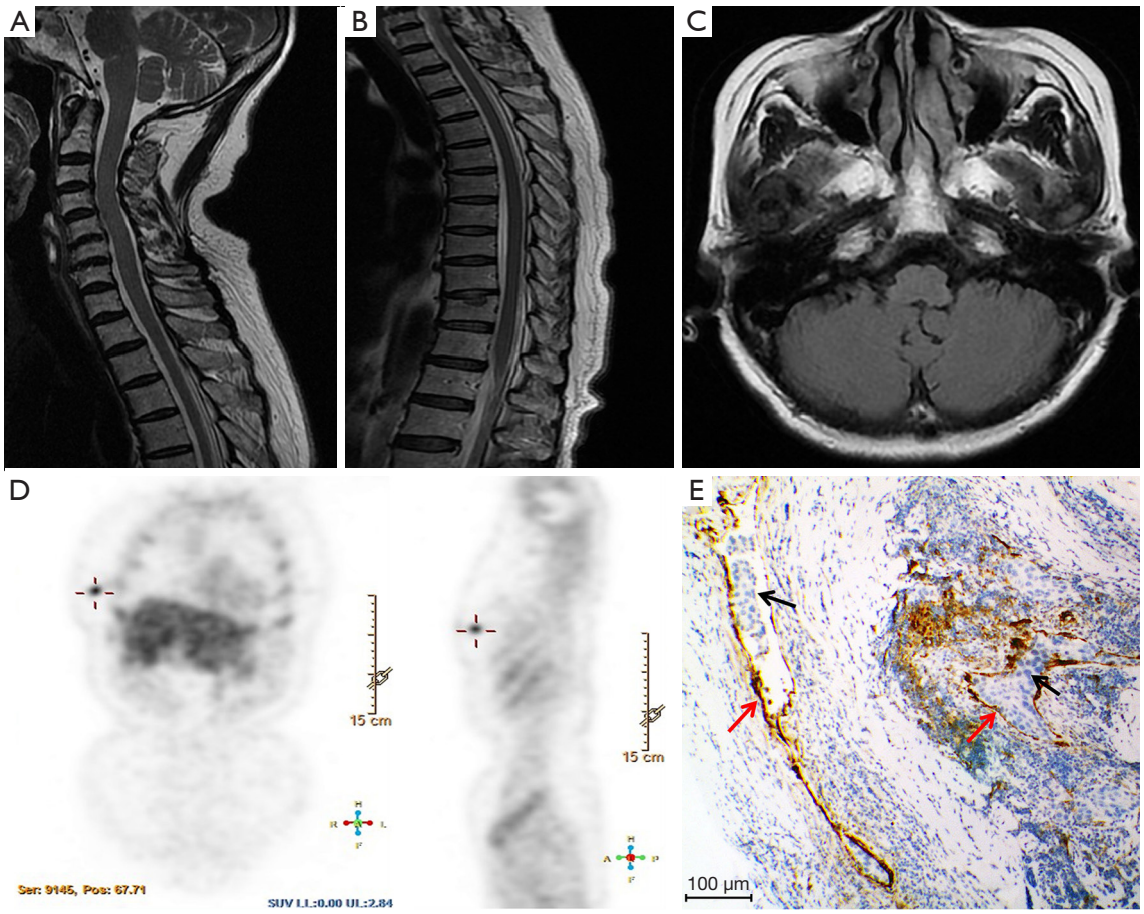

Figure 1 Radiological and histological images of the patient. (A) T2 MRI of the cervical spinal cord showed normal structure. (B) T2 MRI of the thoracic spinal cord revealed no abnormal signal. (C) FLAIR sequence of the brain stem and cerebellum did not indicate any abnormalities. (D) ^{18}F-FDG-PET scan detected increased FDG activity in the upper external quadrant of the right breast. (E) Histological staining demonstrated tumor emboli invading the lymph cavity, indicated by black arrows. Healthy cell nuclei and enlarged cancer cell nuclei were stained blue with hematoxylin. Lymph vessels, stained brown after D2-40 immunostaining, were visible (red arrows). H, head; F, foot; R, right; L, left; T2 MRI, T2-weighted magnetic resonance imaging; FLAIR, fluid attenuated inversion recovery; PET, positron emission tomography; ^{18}F-FDG, ^{18}F-fluorodeoxyglucose.

acidic protein (GFAP) in the CSF and serum samples of the patient. A semi-quantitative line immunoassay (including anti-CV2/CRMP-5, anti-amphiphysin, anti-Ma1, anti-Ma2, anti-Ri, anti-Yo, anti-Hu, anti-SOX1, anti-GAD65, anti-DNER, anti-Zic4, anti-protein kinase Cγ (PKCγ), anti-Recoverin, and anti-Titin) was performed on the serum to test for paraneoplastic antibodies, which showed a slightly positive result for anti-CV2/CRMP-5 antibody [13 arbitrary units (AU); normal range <5 AU]. The patient was treated with intravenous immunoglobulin (0.4 g/kg/day) for five days but did not respond well. Positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG) displayed pathological ^{18}F-FDG uptake in the external upper quadrant of the right breast (*Figure 1D*). Subsequently, pathological examination of the breast biopsy revealed stage II invasive ductal carcinoma (*Figure 1E*). A modified radical mastectomy for breast cancer was carried out, and the presence of human epidermal growth factor receptor 2 (HER2) in the cancer tissue in situ was established. The patient had 4 sessions of doxorubicin hydrochloride liposome with cyclophosphamide 3 weeks after surgery. Then, she had trastuzumab monotherapy for 9 months after receiving 4 cycles of targeted therapy with paclitaxel and trastuzumab every 3 weeks. Over the ensuing months,

her symptoms improved dramatically. By October 2, 2022, she was able to walk normally again, while only a slight amount of numbness persisted in the distal ends of both feet. She regained her capacity to travel by bicycle and live independently.

Discussion

The patient primarily exhibited subacute spinal cord syndrome, characterized by gradually worsening lack of coordination, signs of damage to the nerve pathways, and abnormal sensations in both the limbs and trunk. These symptoms appeared without any indication of metabolic (such as deficiencies in vitamin B12 or copper), infectious, inflammatory, hereditary, toxic, or vascular diseases. Spinal MRI scans did not reveal any noteworthy changes, and tests for AQP4, MOG, and GFAP antibodies in the blood came back negative, ruling out a diagnosis of NMOSD. However, the presence of anti-CV2/CRMP5 antibodies in the bloodstream and the presence of a hypercoagulable state indicated a paraneoplastic cause, leading us to suspect and ultimately confirm a diagnosis of breast cancer. The patient's lack of urinary and bowel dysfunction suggested that the damage to the spinal cord was incomplete and did not align with the typical findings of transverse spinal cord injury seen in most paraneoplastic NMOSD cases using MRI. Surprisingly, there was a significant improvement in the patient's coordination and abnormal sensations following effective anti-tumor treatment, which confirmed the diagnosis of PNM.

In 1897, Lubarsch first suggested a potential link between malignancies in the internal organs and myelopathy. Subsequently, there were occasional reports of a few cases where patients with tumors experienced necrotizing myelopathy. Autopsy findings revealed signs such as spinal swelling, degenerative changes, necrosis, and macrophage infiltration. From the 1990s onwards, the autoimmune mechanism of PNM has been widely acknowledged. It is believed to be triggered by shared antigens between a tumor and the nervous system. This understanding has played a significant role in the identification of specific onconeural antibodies in patients with cancer through serological testing. A positive serologic rate of 81% has been noted for PNM, a disorder affecting the spinal cord and frequently linked to autoantibodies in the nucleus and cytoplasm of the neurons (7). Lung and breast carcinomas are the malignancies that are most frequently associated with this kind of myelopathy (11). Three groups of reported cases of PNM have been identified in literature: (I) paraneoplastic neuromyelitis optica spectrum disorder (PNNMOSD) with AQP4-Ab positivity; (II) paraneoplastic autoimmune myelopathy (PNAM) linked to a particular onconeural antibody; and (III) PNM without onconeural antibodies detected. It is advised to routinely perform serological testing for onconeural antibodies in patients with unexplained myelopathy or those who do not demonstrate a serological response for AQP4-Ab in order to determine the paraneoplastic etiology of autoimmune myelopathy (12). More than 40 cases of PNNMOSD with myelitis and optic neuritis that tested positive for AQP4-Ab over the past 20 years (9) suggest a rare possibility for NMOSD to display paraneoplastic tendencies, even when it presents with typical clinical symptoms, indicating a novel paraneoplastic phenomenon. These AQP4-Ab positive patients with PNNMOSD were all found to have severe longitudinal spinal cord lesions (13). The incidence of longitudinally extensive transverse myelitis detected through spinal MRI scans as an initial symptom in patients with PNNMOSD was found to be similar to those without paraneoplastic NMOSD (7). PNAM, which is a rare subtype of PNM, shares some clinical and MRI characteristics with PNNMOSD (9,12).

Currently, information about the clinical and imaging characteristics of patients with PNM has been gathered from three clinical studies conducted at the Mayo Clinic (7,14,15). In a groundbreaking and extensive series of studies involving 31 cases of isolated PNM linked to specific onconeural antibodies or specified cancers, researchers detected T2 MRI signal abnormalities in 65% of patients (16). These abnormalities were observed in various forms, including longitudinally extensive signal abnormalities (45%) and symmetrical abnormalities specific to certain regions of the spinal cord, such as the longitudinal tracts or gray matter (48%). The presence of such abnormalities in the lateral column, dorsal column, central gray matter, dorsal and lateral column, or the dorsal column and gray matter strongly indicate the likelihood of PNM. However, 35% of patients with PNM did not exhibit notable abnormalities on spinal cord MRI scans (7). Similarly, a previous retrospective study conducted at the Mayo Clinic on autoimmune myelopathy associated with CRMP5-Ab IgG revealed that most patients had T2 signal abnormalities, with 42% of them displaying longitudinally extensive lesions (17). Additionally, a significant proportion (41%) of patients had a normal spinal cord structure in their MRI scans (12,17).

Misdiagnoses have been common in cases of CV2/

CRMP5-related autoimmune myelopathy. This is mainly due to various types of idiopathic inflammatory demyelinating disorders or unspecified neurodegenerative myelopathy when no abnormalities are detected on the spinal cord as shown by MRI. The patient in the current study was initially believed to have an unusual subacute degeneration of the spinal cord, potentially linked to a deficiency in vitamin B12 since the spinal cord MRI did not indicate any problems. However, a different diagnosis was considered when the patient did not show improvement even after receiving vitamin B12 treatment for more than a month, and when electromyography did not reveal the typical signs of peripheral nerve injury.

The majority of patients with PNAM experienced a gradual progression of symptoms, either in a subacute (52%) or insidious (48%) manner. Acute transverse myelopathy, on the other hand, was rarely observed in patients. PNAM, which is associated with CV2/CRMP5 Ab-IgG, was more prevalent in older individuals and smokers. It frequently occurred alongside other neurological impairments in these populations. The presence of anti-CV2/CRMP5 antibodies was first detected in the serum of 11 patients diagnosed with PNS disorders (14). Laboratory techniques revealed the expression of CV2/CRMP5 antigen in the cytoplasm of oligodendrocytes in the white matter of various regions in the adult rat brain, including the brainstem, cerebellum, and spinal cord. Strong positive staining for anti-CV2/CRMP5 antibodies was observed in several areas, including the pyramidal tract, spinal tract of the trigeminal nerve, medial longitudinal fasciculus of the brainstem, cerebellar peduncles, cerebellar white matter, all spinal cord tracts, and the optic chiasm (14). Additionally, the antibodies were detected in the dorsal root ganglion and peripheral nerve axons. A significant number of patients with CV2/CRMP5-IgG-related PNAM (41%) exhibited other neurological impairments, such as cerebellar ataxia and optic neuritis/retinitis (16). Peripheral neuropathy was the most common neurological impairment (57%) (15,17,18). In the current case, the patient displayed progressive ataxia and a positive Romberg's sign, likely due to immune attack on the contralateral spinocerebellar tract and dorsal funiculus. The CMAP and SNAP amplitude values of the patient were slightly below the threshold, suggesting the presence of paraneoplastic peripheral neuropathy in addition to spinal cord injury.

The present instance exhibited neurological impairment resulting from PNM, which could potentially improve after undergoing anti-cancer treatment. Paraneoplastic etiology should be considered for patients who encounter unexplained myelopathy or had normal results in spinal MRI. We advise conducting routine serological testing for onconeural antibodies, such as CV2/CRPM5, in patients with myelopathy whose origins are unknown or who have AQP4-Ab-negative serological findings. Radiological examinations, in particular PET scans, can help find hidden cancers and aid in the paraneoplastic syndrome diagnosis.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-22-1263/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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