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Clinical Case Report

A case of anti-Yo antibody positive subacute cerebellar degeneration presenting as acute cerebrovascular disease in an undiagnosed breast cancer patient

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Abstract

A 41-year-old female patient presented initially with right limb ataxia, which resembled the clinical process of acute cerebrovascular disease. However, no obvious acute infarction was found on Cranial MR2. The patient's symptoms did not significantly improve after treatment with antiplatelet aggregation, stabilizing plate, clearing oxygen free radicals, and improving circulation. The patient was later diagnosed with subacute cerebellar degeneration by detecting Paratumor-related antibodies in cerebrospinal fluid and blood. Further investigation by PET-CT scan of the whole body revealed a breast tumor.

Keywords: Acute cerebrovascular disease; Subacute cerebellar degeneration; Ataxia; Breast cancer.

1. Introduction

Subacute cerebellar degeneration (SCD) is a nervous system syndrome characterized by cerebellar ataxia by tumor-induced autoimmunity against cerebellar antigens, also known as paraneoplastic cerebellar degeneration (PCD). It is a rare non-metastatic neurologic complication.

Paraneoplastic cerebellar degeneration (PCD) is the nervous system's most common paraneoplastic syndrome (PNS), accounting for about 5. 9%-37% of PNS. It is most common in small cell lung cancer but can also be seen in other malignant tumors such as ovarian cancer and lymphoma.

Clinical manifestations: Subacute or chronic disease course, progressive aggravation, adult women are more common, Neurological symptoms are often bilateral, the first symptoms are gait instability, ataxia, can be accompanied by dysarthria, vertigo, nausea, vomiting, Pyramidal tract sign, extrapyramidal system changes, psychiatric symptoms, cognitive disorders, Early MRI and CT are normal, CSF lymphocytes are mildly elevated, as are protein and lgG Antibodies to Hu, Yo, PCA-TR and mGluR1 can be detected in serum and cerebrospinal fluid.

The treatment of PCD is based on the detection of the primary tumor and early surgical treatment, plasma exchange has been reported to stabilize the disease. However, in some cases of anti-YO antibody positive, immune therapy is ineffective, and there is no significant improvement of neurological symptoms in treating primary disease.

2. Presentation

A 41-year- old female presented to Taiyuan Central Hospital on December 8, 2021, due to 'unfavorable' movement of the right limb and disfluency in speech for three days. Three days before admission, the patient had been weak on right limb, disfluency speech, intermittent dizziness, anorexia, fatigue, no headache, nausea, vomiting, tinnitus, numbness or tingling of the right lower limb, loss of consciousness or other symptoms. The patient was admitted to our department for proposed "acute cerebrovascular disease" for further diagnosis and management. Since the onset of the disease, the patient had a poor mood and a decreased appetite, with normal bowel and bladder function.

The patient's past medical history includes hospitalization on August 2, 2021, due to weakness of her left limb and numbness of her left facial. She was diagnosed with cervical spondylosis with cerebral infarction, hypertrigly-

ceridemia, hyper homo cysteinemia and vitamin B12 deficiency. After discharge, she was prescribed atorvastatin calcium tablets, Mecobalamin tablets, folic acid tablets and vitamin B6 tablets orally and stopped taking them for over ntwo months. She has denied risk factors for cerebrovascular disease, including hypertension and diabetes mellitus. Denied the history of exposure to poisons and certain drugs and denied the history of drinking and vitamin E deficiency. Additionally, the patient had no recent infection, diarrhoea or fever history.

Physical examination findings include – afebrile, pulse 74 bpm, respiratory rate 16/minute, and blood pressure 118/74mmHg with no postural drop. A full neurological examination was performed. Positive findings include decreased speech fluency with poetry-like expression in language. The patient demonstrated ataxia and dysmetria of the R) arm and R) leg performing finger-nose and heel-shin tests. Her gait was ataxic, and she had difficulty to stand steady with both eyes closed.

Otherwise, she was alert and orientated with memory and calculation unimpaired. Bilateral pupils were equal in size with a diameter of 0.30 cm and reactive to light. No nystagmus or diplopia was observed. The binaural hearing test was normal. Bilateral frontal striae, eye fissure, and nasolabial groove were symmetrical, pharyngeal reflex present, and tongue not deviated. Muscle strength and tone were normal and symmetrical in both arms and legs. Bilateral biceps brachii tendon reflex was slightly brisk (+++), and the bilateral knee tendon was brisk (++++). The Bilateral Babinski sign was negative. The neck was soft with no resistance.

3. Diagnosis and treatment process

Laboratory examination after admission: blood cell analysis, liver and kidney function, electrolyte, blood glucose, glycosylated hemoglobin, vitamin B12, folic acid, blood lipid, D-dimer, myocardial zymogram, n-terminal-b-type natriuretic peptide precursor, thyroid function was not significantly abnormal, coagulation profile was normal, no obvious abnormality was found in routine urine test. Additional blood investigations were carried out, which revealed no obvious abnormality. These included ferritin, rheumatoid factor, anti-streptolysin O, immunoglobulin G, complement C3, complement C4, serum human chorionic gonadotropin, C-reactive protein, anti- neutrophil cytoplasmic antibody, anti-neutrophil cytoplasmic antibody, anti-protease three antibodies, anti-myeloperoxidase antibody, anti-glomerular basement membrane antibody, hepatitis B virus surface antigen, hepatitis A virus IgM antibody, hepatitis E virus IgM antibody, Treponema pallidum specific antibody, hepatitis C virus antibody, human immunodeficiency virus antibody, erythrocyte sedimentation rate, carcinoembryonic antigen and alpha-fetoprotein.

Ssa/ro60kd was weakly positive (minus), and ssa/ro52kd was positive (+). Growth hormone was <0.05ng/ml, squamous cell carcinoma associated antigen 2.85ng/ml, anti-dsDNA negative (−), nucleosome negative (−), SMDI negative (−), Po ribosome negative (−), histone negative (−), UL snRNP ribonucleoprotein negative (−), ssb/lp negative (−), anti-centromeric antibody negative (−), ScL-70 negative (−), j0-1 negative (−), anti-cyclic citrullinated peptide (anti-CCP) antibody, anti-dsDNA antibody and anti-nuclear antibody showed no obvious abnormality.

Accessory investigations: ECG was normal, thyroid color Doppler ultrasound: “No obvious swollen lymph nodes were found in the bilateral neck of the thyroid gland with ti-rads2 grade.” Abdominal color Doppler ultrasound: “fatty liver, gallbladder, pancreas, spleen, kidneys and portal vein have no obvious abnormalities.” Cervical spine MRI showed cervical spine hyperosteogeny with decreased curvature. C3-7 intervertebral disc herniation: abnormal signal shadow at the left side of C5-6 and the right side of C7, C2-3 intervertebral foramen, and possible perineural cyst. Cranial MRI showed vacuolar sella and hypertrophy of bilateral inferior turbinate. Thoracic MRI showed that the thoracic vertebrae were degenerative. Nerve conduction velocity and

somatosensory evoked potential of both lower limbs suggest abnormal SEP of the right lower limb (central segment). Montreal, cognitive function test showed mild cognitive impairment.

A lumbar puncture cerebrospinal fluid examination was given to further clarify the diagnosis. Cerebrospinal fluid: colorless, transparent, white blood cells $5x10^6$/L, red blood cells 0 $x10^6$/L. Cerebrospinal fluid biochemistry: Cerebrospinal fluid sugar: 3.08mmol/l, cerebrospinal fluid protein: 0.3300g/l, and cerebrospinal fluid chloride: 125.00mmol/l （**see Table 1.** Paratumor-related antibodies screened in cerebrospinal fluid and serum showed that the serum anti-Yo antibody was positive (91) (immunoblot method), and the cerebrospinal fluid anti-Yo antibody was positive (97) (immunoblot method).

Table 1 Cerebrospinal fluid routine and Biochemistry

Items	Result
colorless	transparent
white blood cells	$5x10^6$/l,
red blood cells	0 $x10^6$/l.
cerebrospinal fluid sugar	3.08mmol/l
cerebrospinal fluid protein	0.3300g/l
cerebrospinal fluid chloride	125.00mmol/l

Anti-titin antibody, anti-recoverin antibody, anti-PKC γ Antibody, anti- GAD65 antibody, anti-Zic4 antibody, anti tr antibody, anti Sox1 antibody, anti ma2 antibody, anti MA1 antibody, anti-amphiphysin antibody, anti CV2 antibody, anti-RI antibody and anti-Hu antibody were all (-). (**see Table 2 and Table 3**). Other antibodies tested in this panel were negative and included - serum and cerebrospinal fluid anti GAD65 antibody IgG, anti Zic4 antibody IgG, anti-Tr (Dner) antibody IgG, anti CV2 antibody IgG, anti Homer3 antibody IgG, anti ATP1A3 antibody IgG and anti ARHGAP26 antibody IgG.(**see Table 4**).

The serum para tumor antibodies showed positive anti-Yo antibodies (anti-Purkinje cell antibody type 1 (PCA-1) and classical anti-neuron antibodies). The clinical manifestation was cerebellar degeneration. The positive antibody indicated that the probability of tumor was more than 95%. The main tumor types were ovarian cancer and breast cancer. At present, acquired cerebellar ataxia and the paraneoplastic syndrome were considered in the differential diagnosis.

Due to the above findings, further investigations were conducted to reveal any underlying malignancies. The patient stated she had no history of any cancers.

Table 2: Paratumor-related antibodies in serum

Items	Result	Unit	Reference interval	Method
Anti -Titin antibody	（-）<5	AU	（-）<5	Immunoblotting
Anti-Recoverin antibody	（-）<5	AU	（-）<5	Immunoblotting
Anti-PKC γ Antibody	（-）<5	AU	（-）<5	Immunoblotting
Anti-GAD65 antibody IgG	（-）<5	AU	（-）<5	Immunoblotting
Anti-Zic4 antibody IgG	（-）<5	AU	（-）<5	Immunoblotting
Anti-Tr (Dner) antibody IgG	（-）<5	AU	（-）<5	Immunoblotting
Anti-SOX1 antibody	（-）<5	AU	(-) <5	Immunoblotting
Anti- Ma2 antibody	（-）<5	AU	(-) <5	Immunoblotting
Anti-Ma1 antibody	（-）<5	AU	(-) <5	Immunoblotting
Anti-amphiphysin antibody	（-）<5	AU	(-) <5	Immunoblotting
Anti-CV2(CRMP5) antibody	（-）<5	AU	(-) <5	Immunoblotting
Anti-Hu(HuD) antibody	（-）<5	AU	(-) <5	Immunoblotting
Anti-Ri antibody	（-）<5	AU	(-) <5	Immunoblotting
Anti-Yo antibody	**（+）91**	AU	(-) <5	Immunoblotting

Table 3: Paratumor-related antibodies in cerebrospinal fluid

Items	Result	Unit	Reference interval	Method
Anti -Titin antibody	（-）<5	AU	（-）<5	Immunoblotting
Anti-Recoverin antibody	（-）<5	AU	（-）<5	Immunoblotting
Anti-PKC γ Antibody	（-）<5	AU	（-）<5	Immunoblotting
Anti-GAD65 antibody IgG	（-）<5	AU	（-）<5	Immunoblotting
Anti-Zic4 antibody IgG	（-）<5	AU	（-）<5	Immunoblotting
Anti-Tr (Dner) antibody IgG	（-）<5	AU	（-）<5	Immunoblotting
Anti-SOX1 antibody	（-）<5	AU	(-) <5	Immunoblotting
Anti- Ma2 antibody	（-）<5	AU	(-) <5	Immunoblotting
Anti-Ma1 antibody	（-）<5	AU	(-) <5	Immunoblotting
Anti-amphiphysin antibody	（-）<5	AU	(-) <5	Immunoblotting
Anti-CV2(CRMP5) antibody	（-）<5	AU	(-) <5	Immunoblotting
Anti-Hu(HuD) antibody	（-）<5	AU	(-) <5	Immunoblotting
Anti-Ri antibody	（-）<5	AU	(-) <5	Immunoblotting
Anti-Yo antibody	**（+）91**	AU	(-) <5	Immunoblotting

Table 4 Detection results of cerebellar antibody in serum and cerebrospinal fluid

Items	Result	Reference interval	Method
Anti- GAD65 antibody IgG	(-)	（-）	Immunoblotting
Anti-Zic4 antibody IgG	(-)	（-）	Immunoblotting
Anti-Tr (Dner) antibody IgG	(-)	（-）	Immunoblotting
Anti- CV2 antibody IgG,	(-)	（-）	Immunoblotting
Anti -HOMER3 antibody IgG,	(-)	（-）	Transfection cell method
Anti -ATP1A3 antibody IgG	(-)	（-）	Transfection cell method
Anti -ARHGAP26 antibody IgG	(-)	（-）	Transfection cell method

Abdominal, thyroid, gynecological, double breast ultrasound and chest CT examinations were unremarkable. BI-RADS: left breast solid nodule BI-RADS: Grade 3, BI-RADS: double breast cystic nodule BI-RADS. To further clarify the nature, mammography showed that: Right: BI-RADS: Class III, left: BI-RADS: class LLI. A PET-CT was indicated whereby results showed: Node with increased metabolism in the right breast upper quadrant is considered malignant; a lymph node with increased metabolism in the right armpit Metastases cannot be excluded. A few lymph nodes with slightly increased metabolism in zone II of the left neck are likely due to an inflammatory process.

In summary, the patient was a middle-aged female with subacute onset caused by unilateral limb dyskinesia and ataxia. No obvious acute infarct was found on cranial MRI (**see Fig. 1**). The clinical manifestation was similar to acute cerebrovascular disease. After detecting the anti-Yo antibody in serum and cerebrospinal fluid, it was found that the anti-Yo antibody was positive, which suggested subacute cerebellar degeneration. Further investigations included double breast color Doppler ultrasound, gynecological color doppler ultrasound and PET-CT examination of the whole body, which suggested breast cancer.

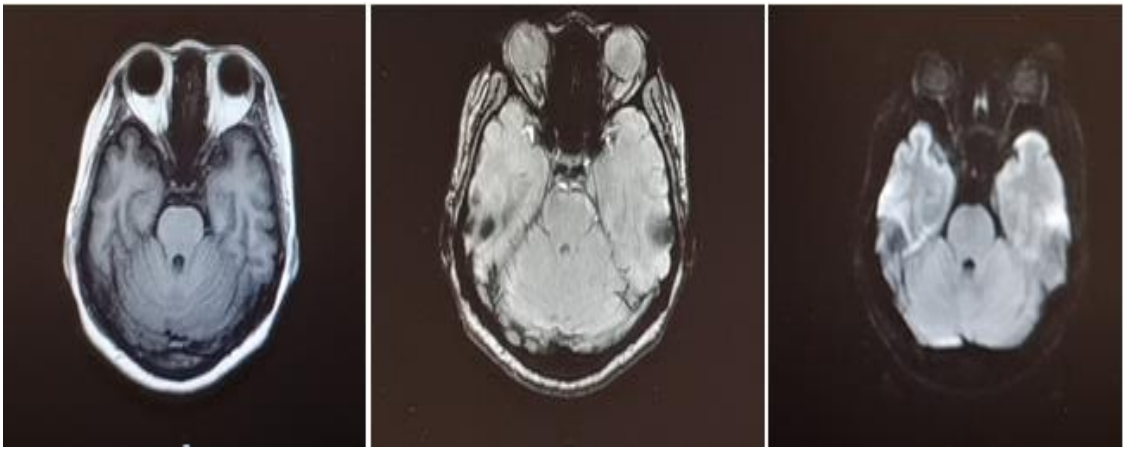

Figure 1 *cervical MRI Equal T1 long T2 signal can be seen in the white matter area under the bilateral frontal-parietal cortex and the right semicircular center, which is high in the FLAIR sequence. No obvious diffusion limit change is found in the DWI sequence, and no abnormal signal is found in another brain parenchyma.*

4. Diagnosis and treatment difficulties

The patient suffered from hemiplegia twice, similar to acute cerebrovascular disease in the clinic. It is easy to be misdiagnosed as a common disease, such as acute cerebrovascular disease, resulting in delayed treatment.

The patient had recurrent ataxia, and obvious signs of cerebellar ataxia can be seen on physical examination. It is easy to diagnose hereditary spinocerebellar ataxia in the clinic, while acquired cerebellar ataxia is ignored.

Anti-Yo antibody was positive in serum and cerebrospinal fluid. Double breast color ultrasound, breast molybdenum target and other examinations might be necessary to investigate further for breast nodules. BI-RADS is grade 3 in our patient. In most clinical cases, patients are recommended to have regular reexamination. But the whole-body PET-CT examination showed breast cancer.

5. Discussion

The patient was admitted to the hospital for 3 days with poor right limb activity and speech fluency. 4 months before admission, she was hospitalized in the local hospital because of "unfavorable left limb

activity" and was diagnosed with "acute cerebrovascular disease". Both attacks were similar to acute cerebrovascular disease, but no obvious imaging evidence was found on MRI.

The positive signs of the patient were a poetry-like language with mild cognitive dysfunction. According to the patient's subacute onset and fluctuating symptoms, mainly involving the spinal cord and cerebellar tract, cerebellar ataxia is considered. The etiology is divided into acquired cerebellar ataxia and hereditary cerebellar ataxia.

Spinocerebellar ataxia is a hereditary disease usually occurring at 30-40 years old. It begins in hiding and takes lower limb ataxia as the first symptom. Upper limb ataxia and dysarthria can also occur in the early stage. Tendon reflex is active in the early stage and weakened in the later stage. Some patients have nystagmus and slow saccade. There may also be dementia, dystonia, Parkinson's symptoms, facial muscle bundle tremor, peripheral neuropathy, etc. Diagnosis mainly depends on genetic testing. The family members of the patients were asked if they had no family history of this disease.

It is suggested that cerebellar ataxia, acquired cerebellar ataxia, and hereditary cerebellar ataxia must be considered simultaneously, and the corresponding antibody tests should be ordered to make a clear diagnosis.

When recurrent diseases are found in the clinical diagnosis and treatment of diseases, we must consider whether they are autoimmune diseases or paraneoplastic syndromes and timely send them for relevant antibody detection.

Paraneoplastic encephalomyelitis damages the lower brainstem, especially the medulla oblongata; dizziness, nystagmus, diplopia, gaze paralysis, dysphagia, dysarthria, ataxia, and even pyramidal tract may occur. Therefore, conducting a lumbar puncture for cerebrospinal fluid analysis and serological paraneoplastic antibody screening is necessary.

Autoimmune diseases such as systemic lupus and erythematosus damage are another important differential. The disease process may involve nervous pathology leading to migraines, epilepsy, cognitive impairment, motor impairment, thoracic spinal cord involvement and lower limb weakness. A complete immune rheumatism series test was completed for our patient, which revealed Ssa/ro60kd

Tracing the patient's family history, it is unlikely that hereditary cerebellar ataxia is the cause. Still, sporadic cerebellar ataxia will not be ruled out, except that one-step gene testing is required. The patient had a vaccination history, so the diagnosis tended to be acquired autoimmune cerebellar ataxia. Therefore, the antibody screening of serum, cerebrospinal fluid paraneoplastic series and cerebellar inflammation series was conducted to make a clear diagnosis.

The anti-Yo antibody (anti-Purkinje cell antibody type 1 antibody) and the classical anti-neuron antibody were positive. Clinically correlating this with the presenting symptoms suggested cerebellar degeneration with main tumor types, likely ovarian or breast.

Nearly 30 autoantibodies have been reported to be related to paraneoplastic carcinoma (PCD), including anti-Yo antibody, anti-Tr antibody, anti-Hu antibody and anti- Ma antibody [1-3]. Anti-Yo-positive cases are the main subtype of PCD, accounting for nearly 50% of all cases [4]. The exact mechanism of Purkinje cell death in anti-Yo antibody-positive PCD is unclear and may be related to the activation of CD8 + T cells. Early pathological changes of anti-Yo antibody positive PCD include perivascular lymphocyte infiltration, microglia activation and CD8 + T lymphocyte infiltration into the Purkinje cell layer of the cerebellum [5, 6]. As the disease progresses, the pathological manifestation of PCD is mainly the rapid loss of non-inflammatory Purkinje cells [7, 8].

PCD with positive anti-Yo antibodies usually presents with symptoms of subacute cerebellar degeneration. The main clinical manifestation is cerebellar ataxia of the trunk and limbs, which lasts for weeks to months [9]. If the patient has dysarthria, nystagmus, diplopia and other symptoms indicating brainstem involvement, the

symptom development will peak within six months without any intervention. Acute onset PCD is relatively rare [9]. Currently, relevant scales are being developed to assess the prognosis of patients [10].

When patients with paraneoplastic antibodies are positive, relevant imaging examinations should be conducted when the serum and cerebrospinal fluid are positive. PET-CT examination of the whole body should be considered to find relevant tumors.

In conclusion, we cannot rule out the symptoms of cerebellar ataxia caused by autoimmune encephalitis, paraneoplastic encephalomyelitis and spinocerebellar ataxia. Therefore, in similar cases seen in clinical practice, we must be vigilant and strive to find the most fundamental reason for the occurrence and development of these symptoms.

Conflict of Interest

The authors declare no conflict of interest

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