

*Case Report***A case of paraneoplastic syndrome definitively diagnosed from progressive ataxia during rehabilitation**

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ABSTRACT

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We report a case of paraneoplastic syndrome (PNS) definitively diagnosed after the patient's previous doctor requested a detailed examination when her ataxia worsened during rehabilitation in the recovery stage. Exacerbation of limb ataxia and positive results for anti-neural antibodies were suggestive of PNS, but no clear neoplastic lesion could be identified on systematic examination, so the patient was admitted to the recovery-stage rehabilitation ward without definitive diagnosis. She underwent another detailed examination when ataxia worsened after starting rehabilitation, leading to a diagnosis of gynecological malignant tumor based on fluorodeoxyglucose positron emission tomography (FDG-PET). The patient underwent hysterectomy and bilateral salpingo-oophorectomy, which confirmed the presence of PNS concomitant with serous adenocarcinoma of the left ovary. Although the numbers are low, patients on recovery-stage rehabilitation wards usually have unstable neurological disorders. Anti-Yo antibody-positive PNS often shows a poor prognosis, and when ataxia worsens after starting rehabilitation, differentiating PNS early to make a definitive diagnosis can influence the prognosis. We report this rare case of PNS.

Key words: paraneoplastic syndrome, ataxia, CA-125, anti-Yo antibody, rehabilitation in recovery stage

Introduction

Paraneoplastic syndrome (PNS) is a diverse syndrome thought to occur as a result of an immunological mechanism in malignant tumor patients with neuropathies. PNS is divided into clinical disease types based on the main symptoms, and in many cases, the characteristic autoantibodies associated with each disease type are detected in the serum and cerebrospinal fluid. Rehabilitation on recovery-stage wards is usually initiated after diagnosis and treatment have been decided, but in the case discussed here, PNS was confirmed following a second detailed examination when ataxia worsened during rehabilitation in the recovery stage. The patient then resumed rehabilitation after tumorectomy until her condition improved and she could be discharged to home.

Subject

The subject was a 50-year-old woman who presented with the chief complaint of an inability to walk. She had no family history of note, but had undergone treatment for acute idiopathic pancreatitis at 26 years old. She was hospitalized for the present illness at Hospital A following the appearance of limb ataxia in March 20XX and subsequent progression of symptoms in April of the same year. Positive findings for anti-Yo antibodies led to suspicion of PNS with gynecologic, breast, and other cancers, although no clear neoplastic lesions were found. Repeated steroid pulse therapy and high-dose intravenous immunoglobulin (IVIg) therapy had no marked effect and the patient was admitted to our center when her functional decline progressed as a result of disuse after becoming bedridden in August of the same year.

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On admission, the patient had a height of 160 cm, body weight of 46.0 kg, body mass index of 18.0 kg/m², blood pressure of 121/77 mmHg, heart rate of 72 beats/min, body temperature of 36.7°C, a regular heart beat and normal respiratory and bowel sounds. Neurological findings were clear consciousness, normal higher brain function and marked scanning and slurred speech. The patient appeared to be aware of mild dysphagia, as she rarely choked when ingesting unthickened fluids. Findings were positive for bilateral gag reflex and tongue protrusion. The finger-to-nose test and heel-to-knee test of coordinated movement revealed marked ataxia predominantly on the left side with decreased muscle tone in the trunk and four limbs. The patient also exhibited mild ataxia of the trunk, but was able to maintain a sitting position. Both superficial and deep sensory systems were normal, as were deep tendon reflexes in all four limbs. Findings were negative for bilateral pathological reflexes and no autonomic nervous symptoms were seen.

Blood testing on admission revealed that levels of tumor marker carbohydrate antigen 125 (CA-125) and antigen sialyl-Tn (STn) had risen to 172.1 U/ml and 46.7 U/ml, respectively (Table 1). Results of a general urine test, electrocardiographic examination and chest and abdominal X-ray examination were all normal. Head computed tomography (CT) revealed no atrophy of the cerebellum or neoplastic lesions, and head magnetic resonance imaging revealed no clear

abnormalities with diffusion-weighted imaging (DWI), T1-weighted imaging (T1WI), T2-weighted imaging (T2WI), fluid attenuation inversion recovery (FLAIR), magnetic resonance angiography (MRA), or gadolinium (Gd) contrast (Figure 1).

In regard to rehabilitation evaluation, total score for the functional independence measure (FIM) was 94 points (motor subscale, 63 points; cognitive subscale, 31 points), Barthel index score was 55 points and Scale for the Assessment and Rating of Ataxia (SARA) score was 20 points. The patient scored 20.5 months on the motor age test (MoA) [1] and had a maximum walking speed over 10 m of 37.4 m/min using a walker. She was able to swallow 4 times in 30 s in the repetitive saliva swallowing test and was rated as Grade 9 according to Fujishima's Grade of Feeding and Swallowing with the ability to consume a regular diet of 3 meals a day.

The patient was able to walk with a walker on admission and could also walk independently between parallel bars during rehabilitation. However, approximately 1 month after admission, ataxia of the four limbs progressed, SARA score worsened to 21.5 points and CA-125 levels rose in a tumor marker test, leading to a request for another detailed examination by her previous doctor in September 20XX and her subsequent transfer. Fluorodeoxyglucose positron emission tomography (FDG-PET) conducted after transfer revealed increased accumulation of FDG in

Table 1. Blood test findings on admission to the recovery ward.

WBC	3.8 × 10 ³ /μl	RBC	3.83 × 10 ⁶ /μl	Hb	12.2 g/dl	Ht	36.3%
Plt	292 × 10 ³ /μl	TP	7.6 g/dl	Alb	4.0 g/dl	TB	0.5 mg/dl
AST	23 IU/l	ALT	21 IU/l	LDH	170 IU/l	ALP	174 IU/l
γGTP	39 IU/l	TC	223 mg/dl	HDL-C	83 mg/dl	LDL-C	118 mg/dl
TG	108 mg/dl	BUN	17.7 mg/dl	Cr	0.4 mg/dl	Na	134 mEq/l
K	3.5 mEq/l	Cl	98 mEq/l	FBS	90 mg/dl	CRP	0.0 mg/dl
CA125	172.1 U/ml	STN	46.7 U/ml				

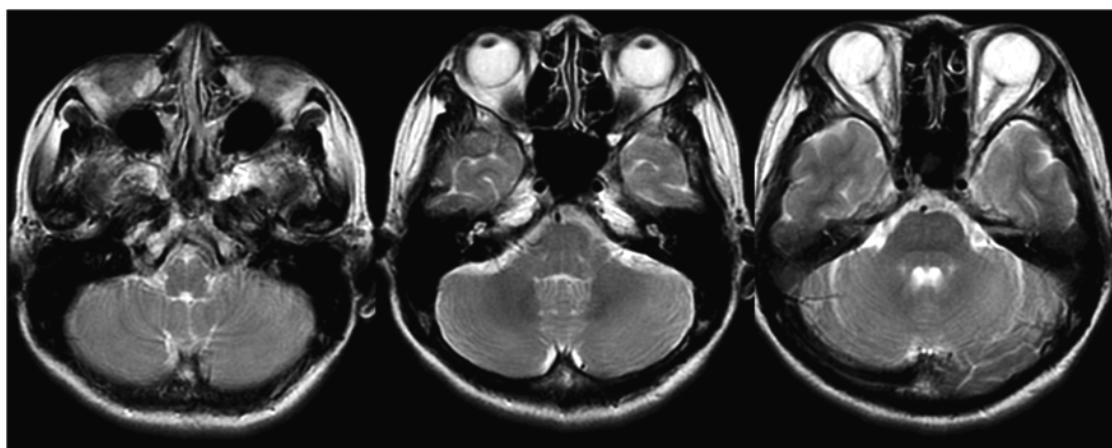


Figure 1. Axial magnetic resonance imaging (T2-weighted) of the head. No clear cerebellar atrophy findings or abnormal signals are seen.

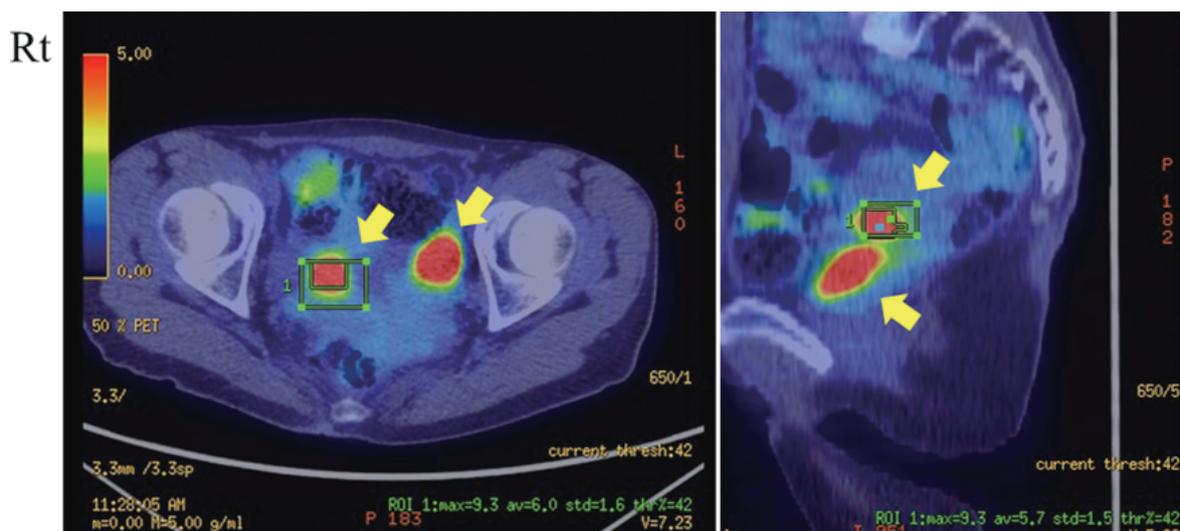


Figure 2. Fluorodeoxyglucose positron emission tomography. Increased accumulation of fluorodeoxyglucose is seen in the anterior uterine wall and left ovary, leading to a diagnosis of malignant tumor (yellow arrows).

the anterior uterine wall and left ovary (Figure 2), leading to a diagnosis of malignant tumor. The patient subsequently underwent hysterectomy and bilateral salpingo-oophorectomy in the Department of Gynecology in November 20XX. Pathological findings of the excised specimen led to a definitive diagnosis of serous adenocarcinoma of the left ovary with uterine invasion (stage IIa) and the cause of the series of cerebellar ataxia symptoms was diagnosed as PNS with gynecological tumor. No significant improvement of ataxia was seen in the patient, despite performing five rounds of postoperative high-dose IVIg therapy and one round of steroid pulse therapy. The patient was re-admitted to our center in August 20XX+1 for rehabilitation with environmental adjustment, due to her strong desire for home care. Rehabilitation evaluation after re-admission revealed exacerbation in all items, with a SARA score of 24 points. A foot-driven wheelchair was thus deemed the best practical means of moving based on the exacerbation of ataxia. During training, walking between parallel bars was performed with assistance. The final rehabilitation evaluation before discharge revealed improvement, with a total FIM score of 98 points, Barthel index score of 70 points and SARA score of 19.5 points. For recuperation at home, a home evaluation and care conference was held to investigate adjustments to the home environment and the contents of welfare services necessary for discharge. The patient was discharged in December 20XX+1 after home remodeling and determining the content of welfare services (Figure 3).

Discussion

In the criteria by Graus et al. for diagnosing PNS, the pathology is classified into “classical PNS” and

“non-classical PNS” on the basis of initial neurological symptoms, and ultimately diagnosed as either “definite PNS” or “possible PNS” on the basis of tumor and anti-neural antibody pathology [2].

According to these diagnostic criteria, the main neurological symptom of ataxia in the present case was “classical PNS” and corresponded to “subacute cerebellar degeneration.” Since advanced cancer was discovered within 5 years of neurological symptom manifestation, this case was diagnosed as “definite PNS.”

PNS occurs as a secondary pathology in 0.5–1% of all cancer patients, 60% of whom are diagnosed with PNS before cancer. This often leads to rapid progression of cerebellar ataxia, resulting in irreversible neuropathies [3]. Moreover, accompanying tumors are usually small and often difficult to detect [4]. In the present case, anti-Yo antibody positivity was confirmed, but no accompanying malignant tumor was found. However, treatment was necessary, so rehabilitation was initiated without definitive diagnosis.

Anti-Yo antibodies are a type of autoantibody seen in PNS that selectively impair Purkinje cells located in the cerebellum, and are known to be expressed at high rates with gynecologic and breast cancer [5, 6]. While early excision of the antigen-presenting tumor is preferred in order to inhibit disease progression, this is often difficult. Progression of cerebellar symptoms after starting rehabilitation and exacerbation of tumor markers in the present case prompted a request for another detailed examination of the malignant tumor.

No previous reports have discussed PNS treatment in recovery-stage rehabilitation wards and none have examined definitive cases of PNS after admission to recovery wards.

Rehabilitation on recovery-stage wards usually

	FIM	94	102	89	98
	BI	55	60	45	70
	SARA	20	21.5	24.0	19.5
Rehabilitation	MoA	20.5	20.5	10	10
evaluation	RSST	4	5	2	2
	Swallowing Gr	9	9	8	8

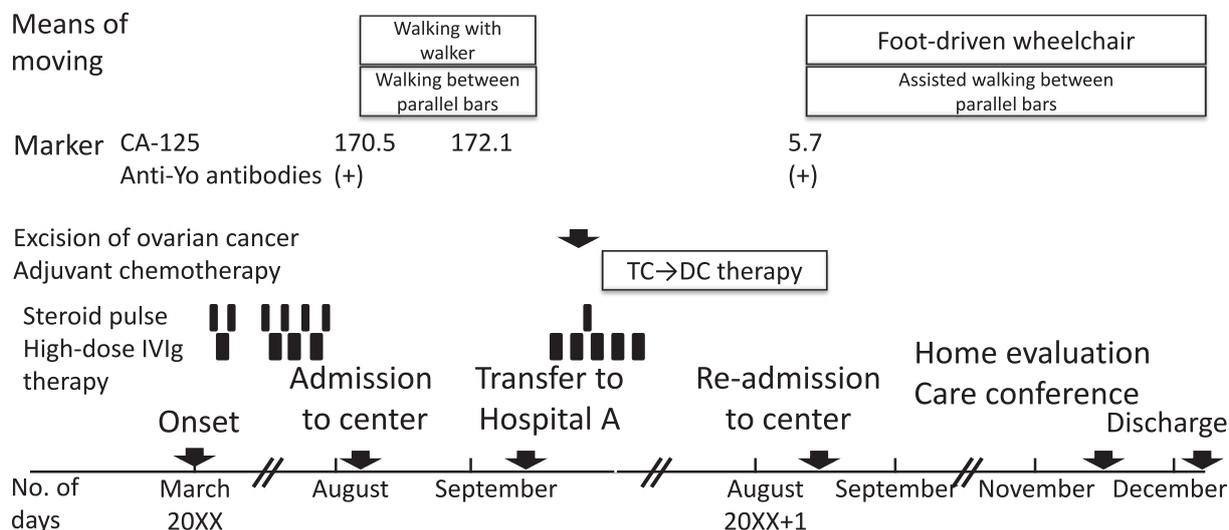


Figure 3. Clinical course.

starts once a definitive diagnosis has been reached. However, rehabilitation must be started without definitive diagnosis in a number of cases, as in the present case. According to an investigative report by the Kaifukuki Rehabilitation Ward Association [7], the majority of patients on recovery-stage rehabilitation wards have diseases of the cerebrovascular system and are discharged after making a functional recovery if rehabilitation can be implemented without a marked change in their general condition.

Meanwhile, rehabilitation for less-common neurodegenerative diseases is also performed on recovery-stage rehabilitation wards. The acute-stage treatment period for many of these diseases can often span a long time, so these pathologies are classified as disuse syndrome while on the recovery-stage ward [7]. When progressive neurodegeneration results from an immunological mechanism [3] as in the present case, caution is required because, unlike many cases where functional recovery is possible, patients exhibit worsening physical function in rehabilitation evaluations while hospitalized on the recovery-stage ward.

Among the types of PNS, anti-Yo antibody-positive PNS is often reported to show particularly poor prognosis [6]. Thus, when cerebellar symptoms progress after starting rehabilitation despite the assumption of a neurodegenerative disease, sufficiently detailed examination is required, including autoantibody tests for anti-Yo antibodies and other antibodies, and systematic CT and PET when accompanying malignant tumor is

suspected.

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