Case Report

The early diagnoses and treatment of anti-Yo antibody-mediated paraneoplastic cerebellar degeneration in a patient with breast cancer: a case report

Wei Wang, Hongjin Liu, Yinhua Liu, Qian Liu

Breast Disease Center, Peking University First Hospital, Beijing, China

Correspondence to: Prof. Qian Liu. Peking University First Hospital, No. 8 Xi Shi Ku Street, Xi Cheng District, Beijing 100034, China. Email: 06744@pkufh.com.

Background: Paraneoplastic cerebellar degeneration (PCD) is a relatively rare complication among patients with cancers with nonmetastatic tumor manifestation, including breast cancer. A breast cancer diagnosis is usually made several months (or even years) after the onset of neurological symptoms.

Case Description: In this study, we describe the early diagnosis and treatment of PCD in one patient with breast cancer. The patient's first symptom was unsteady gait, followed by dizziness and dysarthria of explosive speech. Subacute progressive ataxia symptoms, weight loss, normal imaging findings, and a lack of evidence of infection combined to lead to clinical diagnosis of PCD, and further confirmed by positron emission tomography-computed tomography (PET-CT), positive anti-Yo antibodies and core needle biopsy. Immunosuppressant therapy consisting of intravenous immunoglobulin (IVIG) and high-dose corticosteroids was effective. The patient underwent modified radical mastectomy and 2 cycles of chemotherapy, and the result suggested that treatment of the primary tumor also improved the neurological symptoms to a certain extent. At 1-year follow-up, there was no evidence of recurrence, and the patient's neurological symptoms were stable.

Conclusions: Once PCD was suspected, without clear physical findings or symptoms, PET-CT should be performed for a systemic evaluation for an occult malignancy. Even if the diagnosis and treatment were timely, expectations for prognosis should not be too high.

Keywords: Breast cancer; paraneoplastic cerebellar degeneration (PCD); autoimmunity; case report

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Introduction

Paraneoplastic neurological syndrome (PNS) describes a rare neurological complication among cancer patients with non-metastatic tumor manifestations, usually associated with onconeural autoantibodies. Paraneoplastic cerebellar degeneration (PCD) accounts for 24.3% of PNS cases (1), and is characterized by subacute cerebellar ataxia, including trunk and limb ataxia, vertigo, nystagmus, diplopia, and dysarthria. Primary tumors associated with PCD have been reported in gynecologic malignancies, breast cancer, small cell lung cancer (SCLC) and Hodgkin's lymphoma. Breast cancer diagnosis was usually several months or even years later than the onset of neurological symptoms (2).

The following study describes the early diagnosis and treatment of PCD in a patient with breast cancer (summarized in *Table 1*). We present the following case in accordance with the CARE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-1990/rc).

Case presentation

A 51-year-old woman with no significant history of medical

Table 1 Process of diagnosis and treatment

Day	Symptom	Clinical examination	Diagnosis	Treatment
0	Unsteady gait, followed by dizziness, and dysarthria, rapidly evolved in 2 weeks Weight loss of 8 kg	Normal brain MRI	Unknown	Traditional Chinese medicine
31 (outpatient visit)	–	–	Suspected PCD	–
33 (hospitalization)	Walk against the wall for no more than 100 m; pyramidal signs	–	Suspected PCD	–
35–38	–	PET-CT anti-Yo antibodies (serum++, CSF+++)	Suspected breast cancer	–
40	Stopped deteriorating	–	Confirmed PCD	IVIG; high-dose corticosteroid
47	–	Ultrasound of breast; core needle biopsy	Confirmed breast cancer	–
60	–	–	–	Radical mastectomy
76–97	Improved walking ability	–	–	Chemotherapy for 2 cycles

CSF, cerebrospinal fluid; IVIG, intravenous immunoglobulin; MRI, magnetic resonance imaging; PCD, paraneoplastic cerebellar degeneration; PET-CT, positron emission tomography-computed tomography.

issues, substance abuse, or family history of psychiatric disorders presented symptoms of ataxia. The first symptom was unsteady gait, followed by dizziness and dysarthria of explosive speech. No abnormality was found during magnetic resonance imaging (MRI) of the brain. She was sent home with traditional Chinese medicine treatment. These symptoms rapidly evolved in 2 weeks. She was referred to our institution for further diagnosis and treatment. She could walk against the wall for no more than 100 meters, but displayed no cognitive abnormalities. Physical examination indicated intact strength and sensation, while her cerebellar function was severely impaired. The patient could not complete a rapid alternating movement of the hands test, finger-nose test, or heel-knee-tibia test. In addition, she presented pyramidal signs, including a positive Rossolimo's sign, mandibular reflex, and pouting reflex. In the preceding 2 months, the weight of the patient had decreased by 8 kg. The neurologist considered a diagnosis of PCD due to subacute progressive ataxia symptoms, weight loss, normal imaging findings, and a lack of evidence of infection. Further investigations were conducted to confirm the diagnosis. We found the patient's blood routine, biochemistry, and coagulation to be normal, and all tumor markers [alpha-fetoprotein (AFP), carbohydrate antigen (CA)125, CA19-9, carcinoembryonic antigen (CEA), squamous cell carcinoma antigen (SCC-Ag), neuron-specific enolase (NSE), CA24-2] were within the standard range. In addition, her serum virus antibodies were negative, and cerebrospinal fluid (CSF) routine and biochemistry studies returned unremarkable results. Positron emission tomography-computed tomography (PET-CT) was used to detect potential malignancy, and revealed a high glucose-metabolic occupation in the left breast, as well as increased glucose metabolism on the left cerebellar hemisphere (*Figure 1*). She was also found to have positive serum and CSF anti-Yo antibodies (serum++, CSF+++). About 40 days after the first noticeable symptoms, with the definitive diagnosis of breast cancer related PCD, she was given a 40-g dose of intravenous immunoglobulin (IVIG) on the first day, then 25 g for 4 more days. She was also given 1,000 mg of methylprednisolone sodium succinate, gradually decreased by 50% every 3 days, until a daily amount of 60 mg was being administered. At this point, it was changed to oral prednisone. A few days after the treatment was started, clinical symptoms stopped deteriorating. Ultrasound found a 2.5 cm diameter tumor on the left breast [Breast Imaging-Reporting and Data System (BI-RADs) level 4c], with multiple enlarged axillary lymph nodes.

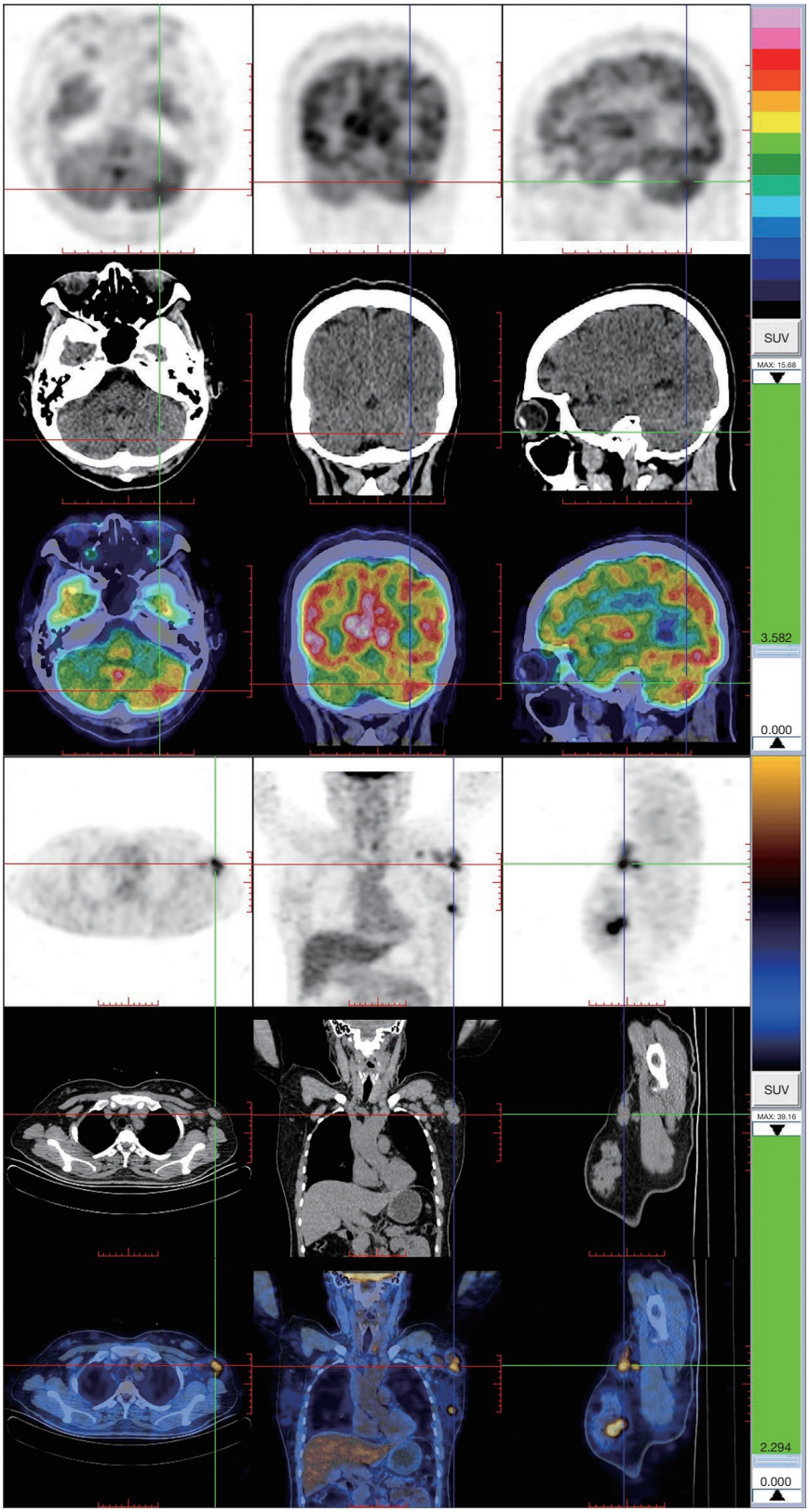

Figure 1 Positron emission tomography-computed tomography image. SUV, standardized uptake value.

A core needle biopsy was performed on the patient and revealed a poorly differentiated breast adenocarcinoma with axillary lymph node metastasis. The tumor was estrogen/progesterone receptor-negative and human epidermal growth factor receptor 2 (HER-2) positive. Due to the coronavirus disease 2019 (COVID-19) epidemic, the surgery was delayed for several weeks. Two months after diagnosis, she underwent modified radical mastectomy (Auchincloss) and had a good postoperative recovery. Pathological staging returned T2N3M0 (stage IIIc). Immunohistochemical staining was consistent with preoperative results. No nerve infiltration was found, while vascular invasion was observed in 2 capsules of lymph nodes.

The original postoperative adjuvant treatments were 6 cycles of adjuvant chemotherapy (paclitaxel, carboplatin, trastuzumab and pertuzumab) every 3 weeks, followed by trastuzumab and pertuzumab for a year. After 2 cycles of treatment, she could stand alone and walk with the support of 1 hand, but always continuously skewed to the left. Her dysarthria also showed no signs of improvement. However, after 2 cycles of chemotherapy, the patient refused to complete additional treatments due to a severe anxiety disorder and side effects. At the 1-year follow-up, there was no evidence of recurrence. Unfortunately, the symptoms of ataxia and dysarthria did not improve although they did not worsen.

All procedures performed in this study were in accordance with the ethical standards of the Institutional Ethics Examining Committee of Human Research of Peking University First Hospital (No. 2019-14) 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.

Discussion

PCD is a rare nonmetastatic brain manifestation and an extremely uncommon complication among breast cancer patients. Its accurate pathogenesis is still unclear, but it is speculated that autoimmunity may be involved. It has been reported that antibodies related to PCD include anti-Yo, anti-Hu, anti-Tr, and anti-Ri, among others, with the highest proportion being anti-Yo. Anti-Yo antibodies, also called anti-Purkinje cell cytoplasmic antibody 1, target a cytoplasmic antigen in the Purkinje cells of the cerebellum, and cause widespread destruction of Purkinje cells. Anti-Yo antibodies have been detected in 1.6% of breast cancer cases, with only a few of these cases eventually developing neurological symptoms (3). In addition, they have also been detected in 5.56% of healthy people (4), leaving the role of anti-Yo antibodies unknown.

Current case reports of breast cancer patients with PCD and positive anti-Yo antibodies have reported an overexpression of HER2 (5-7). In a retrospective study, researchers analyzed the status of HER2 in breast cancer patients with anti-Yo-associated PCD and found HER2 to be overexpressed in 96.3% of the patients (26/27) (8). Furthermore, HER2 overexpression was found in about 20% of breast cancers. From this, we can hypothesize that HER2 overexpression is a risk factor for PCD, but the underlying mechanism requires further study. Oncology staging does not seem to be related to the occurrence of PCD since even a micro-invasive tumor can lead to PCD (9). Other clinical factors, including vascular cancer embolus and perineural invasion, have not been found to be related to the occurrence of PCD.

The clinical symptoms of PCD are diverse, but are mainly characterized by cerebellar dysfunction, including trunk and limb ataxia, vertigo, nystagmus, diplopia and dysarthria. Cognitive impairment is visible in some 20% of patients with PCD (10). Normally, the condition usually initially progresses in an unstoppable manner over several weeks (and for up to 6 months) (10), before reaching a plateau stage where it remains for a long period of time. In the plateau stage, most patients cannot walk independently, or are even completely bedridden. In a case series, these neurologic manifestations were found to precede the diagnosis of breast cancer in 77% or more of cases, and the advancement time was between 2 and 41 months (2), corresponding with most case reports.

When the diagnosis of a PNS is made, it is urgent to screen for occult malignancy. In women, SCLC, ovarian and breast cancer are typical tumor associated with PCD. For patients with specific antibodies and neurological syndrome, clinicians can speculate cancer type, and choose appropriate image examination (11). For patient with rapidly progressive neurological symptoms and without antibody results, our case suggested a thorough PET-CT scan enables early diagnosis.

Owing to the rarity of PCD in breast cancer patients, no related prospective studies have been performed. Treatment options are limited, and usually consist of oncologic and immunological treatments. According to current study, the two treatments are equivalent for maintaining neurological

symptoms. Treatment of tumor could reduce antigen presentation, thereby reducing the autoimmune response. These effects are not immediate, and treatment of tumor does not substitute acute immunotherapy.

The surgical procedures on breast and axilla depend on the stage of the primary tumor, and suitable adjuvant chemotherapy, endocrine therapy and radiotherapy are also necessary. Whether neoadjuvant therapy is suitable for these patients remains unknown. Regarding the existence of autoimmunity, the elimination of the primary lesions may be helpful, yet neoadjuvant therapy is usually not applied. In fact, neoadjuvant therapy has only been used in a few cases (12).

Immunotherapy treatments, such as IVIG, plasmapheresis, corticosteroids, and cyclophosphamide have been used individually or in combination to treat PCD, with only isolated reports detailing a temporary improvement of neurological symptoms (6). A descriptive report analyzed 15 cases of autoantibody-mediated PCD treated with either IVIG alone or combined with other therapies. They found that patients treated with IVIG within 1 month of onset of symptoms were more likely to benefit. The patients that received treatment between 1 and 3 months after symptom onset often achieved stable disease. Beyond 3 months, patients had a poorer prognosis (13). These results suggest that the sooner IVIG is used, the better the outcome.

Unfortunately, despite the relatively good prognosis of breast cancer, neurological symptoms may not improve in most cases, and even continue to progress and deteriorate. Among all anti-Yo antibody positive patients, only 21% retain the ability to walk (14). In a case series of 34 patients with gynecologic tumors or breast cancer, 29% died due to a worsening neurological condition (15). In the case report described here, despite the timeliest diagnosis and treatment of the patients, the prognosis was still not satisfactory. We found that the expectations for prognosis should not be too high, and clinicians need to inform patients and their families of this in advance.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-1990/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-1990/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 Ethics Examining Committee of Human Research of Peking University First Hospital (No. 2019-14) 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.

References

1. Giometto B, Grisold W, Vitaliani R, et al. Paraneoplastic neurologic syndrome in the PNS Euronetwork database: a European study from 20 centers. Arch Neurol 2010;67:330-5.
2. Waterhouse DM, Natale RB, Cody RL. Breast cancer and paraneoplastic cerebellar degeneration. Cancer 1991;68:1835-41.
3. Monstad SE, Storstein A, Dørum A, et al. Yo antibodies in ovarian and breast cancer patients detected by a sensitive immunoprecipitation technique. Clin Exp Immunol 2006;144:53-8.
4. Donfrancesco R, Nativio P, Di Benedetto A, et al. Anti-Yo Antibodies in Children With ADHD: First Results About Serum Cytokines. J Atten Disord 2020;24:1497-502.
5. Le May M, Dent S. Anti-Yo antibody-mediated paraneoplastic cerebellar degeneration associated with cognitive affective syndrome in a patient with breast cancer: a case report and literature review. Curr Oncol

2018;25:e585-91.
6. Key RG, Root JC. Anti-Yo mediated paraneoplastic cerebellar degeneration in the context of breast cancer: a case report and literature review. Psychooncology 2013;22:2152-5.
7. Dorn C, Knobloch C, Kupka M, et al. Paraneoplastic neurological syndrome: patient with anti-Yo antibody and breast cancer: a case report. Arch Gynecol Obstet 2003;269:62-5.
8. Rojas-Marcos I, Picard G, Chinchón D, et al. Human epidermal growth factor receptor 2 overexpression in breast cancer of patients with anti-Yo--associated paraneoplastic cerebellar degeneration. Neuro Oncol 2012;14:506-10.
9. Kato N, Hashida G, Konaka K. Rehabilitation for a patient with anti-Yo antibody-positive paraneoplastic cerebellar degeneration caused by breast cancer: A case report and literature review. Medicine (Baltimore) 2017;96:e8468.
10. Peterson K, Rosenblum MK, Kotanides H, et al. Paraneoplastic cerebellar degeneration. I. A clinical analysis of 55 anti-Yo antibody-positive patients. Neurology 1992;42:1931-7.
11. Titulaer MJ, Soffietti R, Dalmau J, et al. Screening for tumours in paraneoplastic syndromes: report of an EFNS task force. Eur J Neurol 2011;18:19-e3.
12. Mirallas O, Rezqallah Arón MA, Saoudi Gonzalez N, et al. Paraneoplastic cerebellar degeneration diagnosed by anti-Yo determination in a young woman with early breast cancer. BMJ Case Rep 2020;13:233863.
13. Widdess-Walsh P, Tavee JO, Schuele S, et al. Response to intravenous immunoglobulin in anti-Yo associated paraneoplastic cerebellar degeneration: case report and review of the literature. J Neurooncol 2003;63:187-90.
14. Shams'ili S, Grefkens J, de Leeuw B, et al. Paraneoplastic cerebellar degeneration associated with antineuronal antibodies: analysis of 50 patients. Brain 2003;126:1409-18.
15. Rojas I, Graus F, Keime-Guibert F, et al. Long-term clinical outcome of paraneoplastic cerebellar degeneration and anti-Yo antibodies. Neurology 2000;55:713-5.

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