sclerosis

MDPI

Case Report

Anti-Yo Paraneoplastic Cerebellar Degeneration and Breast Cancer: A Long Survival of Persistent Cerebellar Syndrome

Gianluca Avino, Fabiola De Marchi *, Roberto Cantello and Letizia Mazzini

Neurology Unit, Department of Translational Medicine, University of Eastern Piedmont, 28100 Novara, Italy
* Correspondence: fabiola.demarchi@uniupo.it; Tel.: +39-3032-1373-3962

Abstract: Paraneoplastic neurological syndromes (PNS) occur in 1–3% of all cancer patients with several cancer-related neurologic diseases involving any part of the nervous system. Paraneoplastic cerebellar degeneration (PCD) is a specific type of PNS characterized by sub-acute cerebellar syndrome with trunk and limb ataxia, dysarthria, diplopia, and vertigo. We report herein the case of a 70-year-old female patient with cerebellar symptoms and transient anti-Yo antibody PCD positivity manifested three years after a breast cancer diagnosis who is currently neurologically stable after an extended follow-up.

Keywords: paraneoplastic; cerebellar; antibodies; case report; breast cancer

Citation: Avino, G.; De Marchi, F.; Cantello, R.; Mazzini, L. Anti-Yo Paraneoplastic Cerebellar Degeneration and Breast Cancer: A Long Survival of Persistent Cerebellar Syndrome. *Sclerosis* **2023**, *1*, 5–8. https://doi.org/10.3390/sclerosis1010002

Academic Editor: Bradley Turner

Received: 15 October 2022
Revised: 20 November 2022
Accepted: 22 November 2022
Published: 29 November 2022

1. Introduction

Paraneoplastic syndromes are uncommon disorders that can develop in people with cancer but are not directly caused by a malignant tumor infiltration. They can affect several systems, including the Nervous System (NS). The cancer diagnosis can precede, be concomitant with, or follow the syndrome's onset, and, in a few cases, the presumed causative neoplasia is not detected even in an autopsy.

Paraneoplastic neurological syndromes (PNS) occur in 1–3% of all cancer patients, with several cancer-related neurologic diseases involving various parts of the NS [1]. Paraneoplastic cerebellar degeneration (PCD) is a specific type of PNS characterized by sub-acute cerebellar syndrome with trunk and limb ataxia, dysarthria, diplopia, and vertigo. It is associated with various auto-antibodies, most commonly the antineuronal antibody anti-Yo (also called Purkinje cell cytoplasmic antibody type 1). The targets of anti-Yo antibodies are Purkinje cells of the cerebellum. Other associated antibodies are anti-Hu, anti-Tr, anti-Ri, and anti-mGluR [2]. The absence of antibodies has been identified in approximately 40% of patients [3]. Currently, there is no effective therapeutic strategy for anti-Yo-associated PCD, and the clinical prognosis is poor.

2. Case Description

We report herein the case of a 70-year-old female patient diagnosed at that age with breast cancer who manifested cerebellar symptoms and transient anti-Yo antibody PCD positivity three years later who is now neurologically stable after an extended follow-up.

She had been diagnosed with estrogen-receptor-positive (ER+) breast cancer and treated by surgery and FEC (5 fluorouracil, epirubicin, and cyclophosphamide) chemo- and radiotherapies, from which she presented a good recovery and a subsequent negative follow-up. Three years after her cancer diagnosis, the oncologist referred the patient to our Neurological Department for a six-month history of progressive unsteady gait and tremors of the upper limbs and head. A physical and neurological examination detected wide-based gait ataxia and the inability to walk tandemly along with Romberg's sign. Bilateral finger-nose and heel-shin dysmetria were present, as were action and postural tremors. Her extremity reflexes were normal, and both plantar responses were flexor. A cranial nerve evaluation detected horizontal nystagmus through a lateral gaze. Her cognitive functions

were intact. Magnetic Resonance Imaging (MRI) of here brain showed mild brain atrophy (Figure 1). A full-body CT scan showed no metastasis. Blood tumor markers were negative. According to the patient's follow-up, the possibility of cancer metastasis could be ruled out. Her routine laboratory tests were normal, though auto-antibody panel was positive for anti-Yo antibodies in the serum (1:256). All other possible causes (toxic, metabolic, vitamin deficiency, and hypothyroidism) were ruled out. A genetic test for SCA (SCA 1-2-3-7-8-10-12-17) was performed with a negative result.

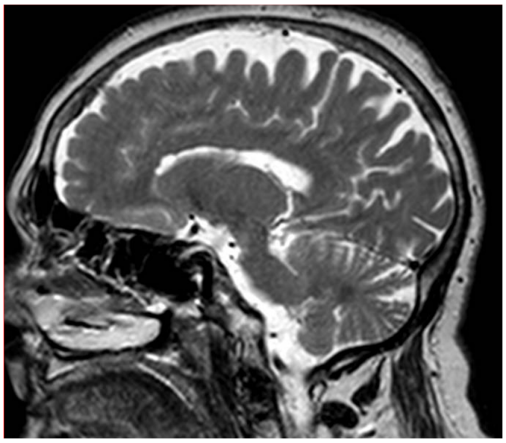

Figure 1. T2-weighted MR sagittal brain image shows mild whole-brain atrophy and mild cerebellum folial atrophy (>postero-superior lobe).

A diagnosis of PCD was made based on the clinical symptoms, the negative brain MRI, and the positive anti-Yo antibodies. Subsequently, the patient was treated with two cycles of intravenous immunoglobulin (IVIg) 0.4 g/kg/day for five days each without noticeable improvement. Her neurological disorder remained stable for two more years. After this period, an increased serum level of CEA and Ca15.3 tumor markers were found. A tumor re-staging with CT total-body bone scintigraphy and total-body Positron Emission Tomography were performed. Bone metastasis was detected. Concomitantly, the ataxic gait, tremor, and dysmetria worsened, with a progressive course. We repeated the brain MRI, which showed diffuse brain and cerebellar atrophy (Figure 2). The patient was successfully treated with bisphosphonates and selective estrogen receptor degrader (SERD). Assays for anti-Yo and other known paraneoplastic antibodies were performed 6 months after the diagnosis of a tumor relapse and were negative. To date, she is neurologically stable with no evidence of a cancer relapse.

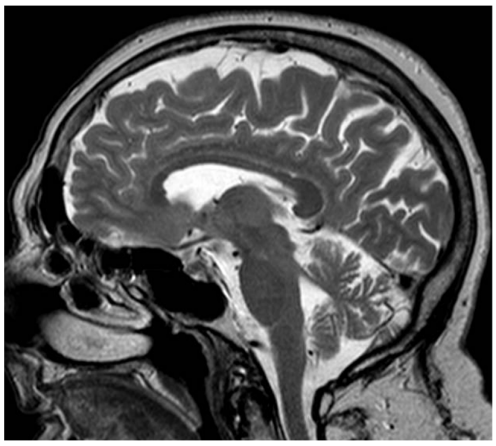

Figure 2. T2-weighted MR sagittal brain image shows an increase in the whole brain and cerebellum atrophy.

3. Discussion

The pathogenesis of PNS is not entirely understood; however, the presence of circulating autoantibodies is a predominant feature of these syndromes. Two types of antibodies can be directed against intracellular antigens (onconeuronal)—such as Hu, Yo, CV2, Ri, Ma, Tr/DNER, amphiphysin, Sox1 [3,4]—or extracellular antigens and can be associated with PCD. Our patient had transient positive antineuronal antibodies of the anti-Yo type. The presence of these antibodies in a female patient presenting with PCD is often associated with breast and gynecological cancer [4–6]. Paraneoplastic symptoms can occur up to 5 years after tumor diagnosis as is described in our case. Anti-Yo antibodies target a cytoplasmic antigen in the Purkinje cells of the cerebellum, and post-mortem examinations exhibit the extensive destruction of Purkinje cells. As a pathogenic mechanism, some evidence suggests an involvement of cytotoxic T-cells [7] that are sensitized by tumor proteins that cross-react with proteins usually expressed by the nervous system. The anti-Yo antibodies recognize a neural protein expressed in the cerebellum's cytoplasm of the Purkinje cells, called CDR2, which is also expressed in breast and ovarian tumors. Therapy directly targeted against anti-Yo is not well established. A review [8] highlighted a clinical benefit in patients receiving IVIg within the first month of the onset of symptoms. The patients treated between one month and three months often had stable disease and the patients treated after three months usually had a poor outcome. It is likely that the absence of tumor recurrence and IVIg treatment allowed for clinical stability. Interestingly, our patient, who started IVIg six months after the onset of cerebellar symptoms, remained neurologically stable for two years until the bone metastases occurred. After their treatment, her neurological symptoms did not worsen, and the patient was clinically stable again. Subsequently, a negative serum antibody titer was found when repeated, which was likely related to the antineoplastic treatment and not the time since the symptom's onset. A negative serum sample is possible in patients with PCD, especially if treated (e.g., by plasma exchange) [9–12], where antibody titers remain undetectable during the follow-up period. Indeed, as demonstrated in our case, tumor treatment remains the best chance for neurological stabilization or improvement [13,14]. In addition, in our patient, even if the antibody serum titer was undetectable later, brain tissue damage was present with evidence of cerebellar atrophy during the MRI follow-up [15,16]. Paraneoplastic cerebellar degeneration usually progresses rapidly, within days or even hours, affecting all limbs and the trunk, and resulting in severe disability. Overall, PCD associated with an anti-Yo antibody has a much poorer prognosis, leading to severe neurologic impairment, immobility, and significantly shorter survival [2]. Moreover, patients with breast cancer have a better prognosis than those with ovarian cancer [16], as supported by our report as well, with a survival greater than 10 years. Despite the clinical progression, the patient is still alive with a mild disability (ataxic gait, a tremor, and dysmetria) and optimal control of systemic neoplastic disease without any involvement of other NS functions. No other cases with such a prolonged survival have been previously reported in the literature.

4. Conclusions

Anti-Yo PCD is a rare, disabling syndrome that worsens the patient's prognosis in terms of their functional ability and survival. Therapies to prevent or reverse the progression of symptoms have been widely unsuccessful. The pathogenesis is still not well-understood, and there are currently no evidence-based treatment guidelines. However, patients such as the one described herein can occasionally be long survivors if the primary tumor is accurately controlled [16].

Author Contributions: Conceptualization and writing—original draft preparation: G.A. and F.D.M.; review and editing and supervision: R.C. and L.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Dalmau, J.; Rosenfeld, M.R. Paraneoplastic syndromes of the CNS. *Lancet Neurol.* **2008**, *7*, 327–340. [CrossRef]
2. Shams'ili, S.; Grefkens, J.; de Leeuw, B.; van den Bent, M.; Hooijkaas, H.; van der Holt, B.; Vecht, C.; Sillevis Smitt, P. Paraneoplastic cerebellar degeneration associated with antineuronal antibodies: Analysis of 50 patients. *Brain* **2003**, *126*, 1409–1418. [CrossRef] [PubMed]
3. Mason, W.P.; Graus, F.; Lang, B.; Honnorat, J.; Delattre, J.Y.; Valldeoriola, F.; Antoine, J.C.; Rosenblum, M.K.; Rosenfeld, M.R.; Newsom-Davis, J.; et al. Small-Cell Lung Cancer, Paraneoplastic Cerebellar Degeneration and the Lambert-Eaton Myasthenic Syndrome. *Brain A J. Neurol.* **1997**, *120*, 1279–1300. [CrossRef] [PubMed]
4. Rojas-Marcos, I.; Rousseau, A.; Keime-Guibert, F.; Reñé, R.; Cartalat-Carel, S.; Delattre, J.Y.; Graus, F. Spectrum of Paraneoplastic Neurologic Disorders in Women with Breast and Gynecologic Cancer. *Medicine* **2003**, *82*, 216–223. [CrossRef] [PubMed]
5. Honnorat, J.; Cartalat-Carel, S.; Ricard, D.; Camdessanche, J.P.; Carpentier, A.F.; Rogemond, V.; Chapuis, F.; Aguera, M.; Decullier, E.; Duchemin, A.M.; et al. Onco-Neural Antibodies and Tumour Type Determine Survival and Neurological Symptoms in Paraneoplastic Neurological Syndromes with Hu or CV2/CRMP5 Antibodies. *J. Neurol. Neurosurg. Psychiatry* **2009**, *80*, 412–416. [CrossRef]
6. Meglic, B.; Graus, F.; Grad, A. Anti-Yo-Associated Paraneoplastic Cerebellar Degeneration in a Man with Gastric Ade-nocarcinoma. *J. Neurol. Sci.* **2001**, *185*, 135–138. [CrossRef] [PubMed]
7. Tanaka, K. Pathogenesis of paraneoplastic neurological syndromes. *Brain Nerve* **2010**, *62*, 309–318. [PubMed]
8. Widdess-Walsh, P.; Tavee, J.O.; Schuele, S.; Stevens, G.H. Response to intravenous immunoglobulin in Anti-Yo associated paraneoplastic cerebellar degeneration: Case report and review of the literature. *J. Neuro-Oncol.* **2003**, *63*, 187–190. [CrossRef] [PubMed]
9. Uchuya, M.; Graus, F.; Vega, F.; Rene, R.; Delattre, J.Y. Intravenous immunoglobulin treatment in paraneoplastic neurological syndromes with antineuronal autoantibodies. *J. Neurol. Neurosurg. Psychiatry* **1996**, *60*, 388–392. [CrossRef] [PubMed]
10. Phuphanich, S.; Brock, C. Neurologic Improvement after High-dose Intravenous Immunoglobulin Therapy in Patients with Paraneoplastic Cerebellar Degeneration Associated with Anti-Purkinje Cell Antibody. *J. Neuro-Oncol.* **2006**, *81*, 67–69. [CrossRef] [PubMed]
11. Hu, F.Q.; Shang, F.R.; Liu, J.J.; Yuan, H. Plasma Exchange for Treating Anti-Yo-Associated Paraneoplastic Cerebellar Degeneration: Case Report and Literature Review. *Medicine* **2020**, *99*, e21760. [CrossRef] [PubMed]
12. Meloni, C.; Iani, C.; Dominijanni, S.; Arciprete, F.; Cipriani, S.; Caramiello, M.S.; Tozzo, C.; Lombardo, P.A.; Tatangelo, P.; Cecilia, A.; et al. A Case Report of Plasma Exchange Therapy in Non-paraneoplastic Cerebellar Ataxia Associated with Anti-Yo Antibody. *Ther. Apher. Dial.* **2004**, *8*, 500–502. [CrossRef] [PubMed]
13. Vedeler, C.A.; Antoine, J.C.; Giometto, B.; Graus, F.; Grisold, W.; Hart, I.K.; Honnorat, J.; Sillevis Smitt, P.A.E.; Verschuuren, J.J.G.M.; Voltz, R.; et al. Management of Paraneoplastic Neu-rological Syndromes: Report of an EFNS Task Force. *Eur. J. Neurol.* **2006**, *13*, 682–690. [CrossRef] [PubMed]
14. Titulaer, M.J.; Soffietti, R.; Dalmau, J.; Gilhus, N.E.; Giometto, B.; Graus, F.; Grisold, W.; Honnorat, J.; Sillevis Smitt, P.A.E.; Tanasescu, R.; et al. Screening for Tumours in Paraneoplastic Syndromes: Report of an EFNS Task Force: Screening for Tumours in PNS. *Eur. J. Neurol.* **2011**, *18*, 19-e3. [CrossRef]
15. Rojas, I.; Graus, F.; Keime-Guibert, F.; Rene, R.; Delattre, J.Y.; Ramon, J.M.; Dalmau, J.; Posner, J.B. Long-Term Clinical Outcome of Para-neoplastic Cerebellar Degeneration and Anti-Yo Antibodies. *Neurology* **2000**, *55*, 713–715. [CrossRef] [PubMed]
16. Rojas, I.; Graus, F.; Keime-Guibert, F.; Rene, R.; Delattre, J.Y.; Ramon, J.M.; Dalmau, J.; Posner, J.B. Paraneoplastic Cerebellar Degeneration. I. A Clinical Analysis of 55 Anti-Yo Antibody-Positive Patients. *Neurology* **1992**, *42*, 1931–1937.